Hepatocellular carcinoma

Alejandro Forner, María Reig, Jordi Bruix

Hepatocellular carcinoma appears frequently in patients with cirrhosis. Surveillance by biannual ultrasound is recommended for such patients because it allows diagnosis at an early stage, when effective therapies are feasible. The best candidates for resection are patients with a solitary tumour and preserved liver function. Liver transplantation benefits patients who are not good candidates for surgical resection, and the best candidates are those within Milan criteria (solitary tumour ≤5 cm or up to three nodules ≤3 cm). Image-guided ablation is the most frequently used therapeutic strategy, but its efficacy is limited by the size of the tumour and its localisation. Chemoembolisation has survival benefit in asymptomatic patients with multifocal disease without vascular invasion or extrahepatic spread. Finally, sorafenib, lenvatinib, which is non-inferior to sorafenib, and regorafenib increase survival and are the standard treatments in advanced hepatocellular carcinoma. This Seminar summarises the scientific evidence that supports the current recommendations for clinical practice, and discusses the areas in which more research is needed.

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Barcelona Clinic Liver Cancer group, Liver Unit, IDIBAPS, Hospital Clínic, University of Barcelona, Barcelona, Spain (A Forner MD, M Reig MD, Prof J Bruix MD); **and Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, Madrid, Spain** (A Forner, M Reig, Prof J Bruix)

Correspondence to:
Dr Alejandro Forner, Barcelona Clinic Liver Cancer group, Liver Unit, IDIBAPS, Hospital Clínic, 08036 Barcelona, Spain
aforner@clinic.ub.es

Introduction

Hepatocellular carcinoma is the most frequent primary liver cancer and is an important medical problem. With 782 000 cases diagnosed and 746 000 deaths in 2012, and an age-adjusted worldwide incidence of 10·1 cases per 100 000 person-years, hepatocellular carcinoma is ranked as the sixth most common neoplasm and the third leading cause of cancer death. Hepatocellular carcinoma has been recognised as a leading cause of death among patients with cirrhosis, and its incidence is expected to increase in the future.[1] Together with the recognition of its clinical relevance, major progress has been made in prevention, detection, diagnosis, and treatment. In this Seminar, we summarise the knowledge that has emerged since our last update in 2012.[2]

Epidemiology

The development of hepatocellular carcinoma is closely related to the presence of chronic liver disease. The worldwide incidence is heterogeneous because of the variable prevalence of the risk factors. Most hepatocellular carcinoma cases (80%) occur in sub-Saharan Africa and eastern Asia, where the main risk factors are chronic hepatitis B and aflatoxin B1 exposure.[3] In patients with hepatitis B, the incidence of hepatocellular carcinoma increases with viral load, duration of infection, and severity of the liver disease.[4] Occult hepatitis B virus infection is also associated with increased risk because of DNA damage induced by virus integration.[5] In the USA, Europe, and Japan, hepatitis C is the main risk factor,[3] together with excessive alcohol intake.[6] The epidemiology of hepatocellular carcinoma is characterised by dynamic temporal trends. In Japan and Europe, where spread of hepatitis C virus occurred earlier than in the USA, the incidence of hepatocellular carcinoma has almost reached a plateau and in some areas it is declining.[7,8] By contrast, in the USA, where hepatitis C virus spread occurred later, the incidence is still increasing and is predicted to stabilise by 2020.[8] Non-alcoholic fatty liver disease is becoming an important cause of hepatocellular carcinoma in developed regions.[9,10] Future prospective studies should clarify to what extent non-alcoholic fatty liver disease overlaps with alcohol-related liver disease as a risk factor for hepatocellular carcinoma.[11] Growing evidence based on retrospective assessments supports the association between metabolic syndrome, diabetes, and obesity and hepatocellular carcinoma in patients with non-alcoholic fatty liver disease. Diabetes is an independent risk factor for hepatocellular carcinoma,[12,13] and liver cancer mortality is five times greater among men with a high baseline body-mass index than among men with a normal body-mass index.[14] Tobacco use is associated with an increased risk,[15] whereas coffee is associated with reduced risk.[16] Co-infection of HIV with either hepatitis B virus or hepatitis C virus might be associated with rapidly progressive liver disease, and the risk of hepatocellular carcinoma increases on cirrhosis development.[17]

Hepatocellular carcinoma-related mortality can be prevented by avoiding the risk factors. Nationwide hepatitis B virus vaccination of infants in Taiwan reduced the incidence of hepatocellular carcinoma per 10^5 person-years from 0·92 in the unvaccinated cohort to 0·23 in the vaccinated birth cohorts.[18] Once chronic infection is acquired, elimination of viral replication by antiviral agents prevents progression of liver disease and probably development of hepatocellular carcinoma.[19] Prevention of hepatitis C virus infection relies on avoiding transmission through contaminated blood. Once infection is acquired, effective antiviral therapy should prevent the progression to cirrhosis and, ultimately, the development of

Search strategy and selection criteria

We searched in MEDLINE, Embase, and Cochrane Library (between Jan 1, 2005, and April 30, 2017), using hepatocellular carcinoma, liver cancer, and primary liver carcinoma as free text words. We also did a manual search and review of reference lists. We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. Only articles published in English were selected.

hepatocellular carcinoma.[20,21] However, if cirrhosis is established, the risk of hepatocellular carcinoma remains despite successful antiviral treatment.[21] The advent of the new direct-acting antivirals has been a major breakthrough because of their high efficacy, but the optimal safety profile should be determined because some studies suggest an increased cancer risk associated with direct-acting antiviral treatment.[22] A recent meta-analysis[23] concluded that occurrence or recurrence of hepatocellular carcinoma is not different between patients receiving direct-acting antivirals and those receiving interferon therapy, but the strength of this analysis was limited because of the inclusion of substantially heterogeneous studies without adequate follow-up for detecting hepatocellular carcinoma. Thus, further information needs to be collected about disease evolution in patients after viral cure.

Promotion of healthy life habits, including decreased alcohol consumption, and prevention of metabolic syndrome could reduce the risk of developing hepatocellular carcinoma.[24] Preliminary studies have suggested that prolonged use of metformin in patients with diabetes, propranolol in patients with hepatitis C virus-related cirrhosis, or statins could be associated with a reduction of hepatocellular carcinoma incidence.[25–27] Confirmatory prospective studies are needed before these agents can be recommended for prevention of hepatocellular carcinoma.

Pathogenesis

Development of hepatocellular carcinoma is a complex multistep process that involves sustained inflammatory damage, including hepatocyte necrosis and regeneration, associated with fibrotic deposition. Risk of hepatocellular carcinoma emerges when cirrhosis is established, and it increases in parallel to progressive liver function impairment. Hepatocellular carcinoma is the result of the accumulation of somatic genomic alterations in passenger and driver genes in addition to epigenetic modifications, which explains its huge molecular heterogeneity. These complex phenomena are reviewed elsewhere.[28] Unfortunately, none of the molecular classifications of hepatocellular carcinoma that have been proposed so far predicts disease progression or recurrence.[29]

Surveillance and diagnosis

Hepatocellular carcinoma surveillance aims to reduce disease-related mortality. Several non-randomised studies have shown that patients who were enrolled into a surveillance programme were diagnosed at an earlier stage, received potential curative therapies more frequently, and had better overall survival than did unenrolled peers.[30] Regrettably, these uncontrolled studies are at risk of biases.[31] A randomised controlled trial[32] of surveillance done in China included 18 816 patients with hepatitis B who were randomly allocated by clusters to a screening group (9373 patients) or to a control (9443 patients) group; patients in the screening group received an α-fetoprotein test and an ultrasonography examination every 6 months. Hepatocellular carcinoma-related mortality was significantly lower in the screening group (83·2 per 100 000) than in the control group (131·5 per 100 000), with a mortality rate ratio of 0·63 (95% CI 0·41–0·98), which indicates that screening every 6 months reduced hepatocellular carcinoma mortality by 37%.[32] Notably, however, study adherence was poor (60%) and the individual analysis was questionable because of randomisation by clusters. A validation trial in the USA or Europe is largely unfeasible: ultrasonography is part of the routine evaluation of patients with liver disease, and the perceived benefit from surveillance would impair recruitment.[33] Although the evidence is not of the highest quality, since the only chance to offer effective treatment with long-term disease-free survival is if the tumour is detected at an early stage through screening programmes, it is difficult to argue against the efficacy of surveillance and efforts should be directed to determine its efficiency.[34]

The decision to enter a patient into a surveillance programme is determined by the risk of hepatocellular carcinoma, life expectancy, and the economic cost to be invested. Since no experimental data exist to indicate what level of risk justifies surveillance, the decision is based on cost-effectiveness models with heterogeneous designs. These models show that surveillance is cost-effective and that its efficacy is dictated by the incidence of hepatocellular carcinoma.[35,36] Accordingly, surveillance is recommended for patients with cirrhosis, irrespective of the aetiology, who would be effectively treated if diagnosed with hepatocellular carcinoma, and for patients with hepatitis B but no cirrhosis, in whom the annual incidence of hepatocellular carcinoma is more than 0·2%.[37,38] The annual incidence in patients with chronic hepatitis C and bridging fibrosis in the absence of cirrhosis might surpass this threshold,[39] and therefore surveillance in those patients can also be recommended.[38] In patients with cirrhosis related to hepatitis C virus, the sustained viral response after treatment does not completely eliminate the risk of hepatocellular carcinoma,[21] and thus surveillance should be maintained.[37,38] The incidence of hepatocellular carcinoma in patients with non-viral chronic liver disease without cirrhosis is not well known so a recommendation cannot be made. The impact of surveillance is difficult to analyse in patients with non-alcoholic fatty liver disease for several reasons. First, the reported incidence of hepatocellular carcinoma is very heterogeneous, ranging from 0·25% to 7·6%.[40] Second, hepatocellular carcinoma develops in non-cirrhotic livers in a substantial proportion of patients.[11] Last, the suboptimal performance of abdominal ultrasonography results in under-recognition of small hepatocellular carcinoma nodules, and treatments with potential survival benefit are not feasible in a relevant proportion of patients because of associated comorbidities.[11] Patients with cirrhosis related to non-alcoholic fatty liver disease should undergo surveillance, but a

recommendation for individuals without cirrhosis cannot be made because the risk of hepatocellular carcinoma in this population is not established. Patients with highly impaired liver function should be evaluated for liver transplantation. If this treatment cannot be offered, surveillance offers no benefit for patients with end-stage cirrhosis because diagnosis will not be followed by effective therapy.

The preferred test for surveillance is ultrasonography. This procedure is well tolerated and widely available, and it has a sensitivity of 60–80% and a specificity of more than 90% when it is done expertly.[41] The use of ultrasonography as a surveillance tool is limited by its operator dependency and its unsatisfactory diagnostic accuracy in clinical practice.[42]

Serum tumour markers are an attractive alternative for surveillance and early diagnosis of hepatocellular carcinoma since they allow a non-invasive, objective, and reproducible evaluation. The most common serological test is α-fetoprotein. Disappointingly, in retrospective case-control studies that evaluated the accuracy of this test in hepatocellular carcinoma diagnosis, even considering the most efficient cutoff (10–20 ng/mL), the reported sensitivities were around 60% and, more worryingly, specificities were 80%.[43,44] Combined use of α-fetoprotein and ultrasonography increases detection rates, but also increases false-positive suspicions and cost.[41,45] Other tumour markers, such as des-γ carboxyprothrombin, lectin-bound α-fetoprotein, glypican 3, Golgi protein 73, and Dickkopf 1, have not provided better accuracy.[43,44,46,47] Recently, a score called GALAD, which includes clinical data (sex and age) and tumour markers (α-fetoprotein, α-fetoprotein-L3, and des-γ carboxyprothrombin), has shown promise, but external validation is needed.[48]

The ideal interval of surveillance for hepatocellular carcinoma is dictated by the assumed rate of tumour growth. On the basis of tumour doubling times described in old series and data from available studies, screening of patients every 6 months is recommended. A 6-month interval is more effective in terms of early detection and survival than a 12-month interval;[49] by contrast, a 3-month interval increases the detection of small nodules but has no impact on survival.[50] Since no data demonstrate that higher risk is associated with faster tumour growth, a 3-month interval in not justified in patients at increased risk.

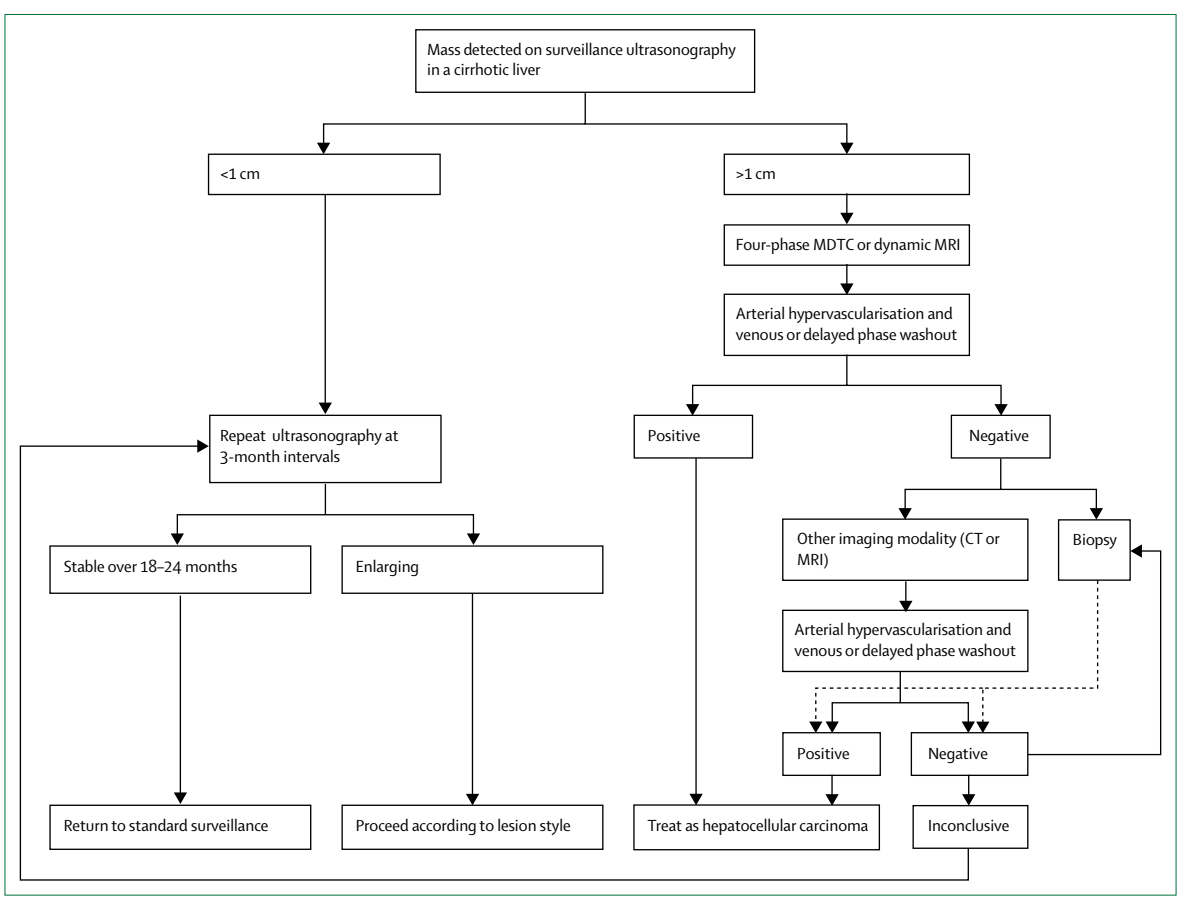

Figure 1: **Diagnostic algorithm for hepatocellular carcinoma**
MDCT=multidetector CT. Modified from reference 37 with permission of John Wiley and Sons.

The unequivocal diagnosis of a nodule detected using ultrasonography in a cirrhotic liver represents a major clinical challenge. Figure 1 summarises the diagnostic algorithm on nodule detection. Nodules with a diameter of less than 1 cm are infrequently diagnosed as hepatocellular carcinoma,[51] and a confident diagnosis of these nodules is almost impossible with current techniques. Even if a hepatocellular carcinoma diagnosis of such nodules were possible, overdiagnosis could occur, which can cause more harm than benefit, as described in other cancer types for which screening is done.[52] In nodules larger than 1 cm, a confident diagnosis of hepatocellular carcinoma can be established using imaging techniques in the setting of liver cirrhosis if the nodule displays a specific imaging pattern. This pattern is defined by intense contrast uptake during the arterial phase followed by contrast washout during the venous phases in contrast-enhanced CT or MRI. The value of these non-invasive criteria for hepatocellular carcinoma in cirrhosis has been prospectively validated.[51,53–55] In nodules between 1 cm and 2 cm, the finding of typical imaging features has a specificity and a predictive positive value of near 100%, and a sensitivity that can reach 71%.[51,53–55] Other parameters such as detection of fatty metamorphosis, isolated hypointensity in venous phases, the presence of a pseudocapsule, or hyperintensity in diffusion-weighted sequences do not increase the diagnostic accuracy of MRI.[56,57] Recently, the American College of Radiology has proposed a system for standardisation of the performance, interpretation reporting, and data collection of CT and MRI examinations of the liver in patients at risk of hepatocellular carcinoma. This system, known as Liver Imaging Reporting and Data System (LI-RADS), stratifies the lesions in five main categories from lesions that are definitively benign (LR 1) to those that are definitively hepatocellular carcinoma (LR 5), so that clinicians can gauge the benefits and risks of proceeding to a more invasive work-up or simply following up the lesions.[58] Prospective MRI evaluation of nodules that are less than 2 cm, detected by ultrasonography during surveillance, has shown that 25% of LR 2 and 69% of LR 3 lesions were hepatocellular carcinoma, and that LR 4 has a specificity of 98·2% for a hepatocellular carcinoma diagnosis.[59] Therefore, distinguishing between LR 4 and LR 5 in nodules detected by ultrasonography has no clinical value.[59]

Contrast-enhanced ultrasonography is not recommended as an imaging technique for non-invasive hepatocellular carcinoma diagnosis because of its inability to differentiate intrahepatic cholangiocarcinoma from hepatocellular carcinoma.[60,61] Additionally, regardless of the contrast pattern, CT or MRI would still be required for staging before treatment.

These non-invasive diagnostic criteria are only valid in patients with cirrhosis. In other clinical scenarios or when imaging fails to display a specific vascular profile, a diagnostic biopsy should be requested. A negative biopsy does not rule out hepatocellular carcinoma, since the false-negative rate of biopsies can reach 30%.[51] An immunohistochemical panel including glypican 3, glutamine synthetase, clathrin heavy chain, and heat-shock protein 70 provides 100% specificity but has suboptimal sensitivity, and might not add to the accuracy of a diagnosis made by an expert pathologist.[62]

Staging and prognostic assessment

Prognostic assessment is a crucial step in the management of patients with hepatocellular carcinoma. Since most patients have an associated liver disease, the prognostic evaluation should incorporate not only tumour stage, but also the degree of liver function impairment. In addition, the presence of cancer-related symptoms has consistently shown a negative effect on survival. Finally, for any system to be clinically successful, prognostic prediction should be paired with treatment indication.[63] Several proposals have been made to stratify patients according to the expected outcome.[64] The most relevant and externally evaluated systems are the Cancer of the Liver Italian Program; Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire; Tumour, Node, Metastasis (TNM); the Chinese University Prognostic Index; Japanese Integrated Staging; the Taipei Integrated Scoring System; and, more recently, the Hong Kong Liver Cancer staging system.[65] The Barcelona Clinic Liver Cancer (BCLC) system has been extensively validated and is the most commonly used staging system for hepatocellular carcinoma. Since its original publication in 1999, it has been updated according to the results of investigations in untreated and treated patients that have incorporated strong evidence that has modified practice. Figure 2 shows the most recently updated version. Patients with very early-stage (BCLC 0) and early-stage (BCLC A) hepatocellular carcinoma have a solitary lesion or up to three nodules that are less than 3 cm in diameter (without macrovascular invasion or extrahepatic spread) and preserved liver function. These patients can benefit from resection, transplantation, or ablation, and for each of these options prognosis can be refined according to different parameters. Patients with intermediate-stage hepatocellular carcinoma (BCLC B) do not have symptoms, but they have large, multifocal tumours without vascular invasion or spread beyond the liver. If liver function is preserved, these patients could be candidates for transarterial chemoembolisation. Patients with advanced-stage disease (BCLC C) have one or more of the following features: tumours that have spread beyond the liver, vascular invasion, and mild cancer-related symptoms (grades 1–2 according to the Eastern Cooperative Oncology Group [ECOG] Performance Status). The tyrosine kinase inhibitors sorafenib and regorafenib are the only systemic treatments that have been found to prolong survival. Lenvatinib has been shown to be non-inferior to sorafenib in first-line treatment, but it targets the same population. Very recently, positive results have been announced for cabozantinib as a second-line treatment, but no detailed information is available yet.[66]

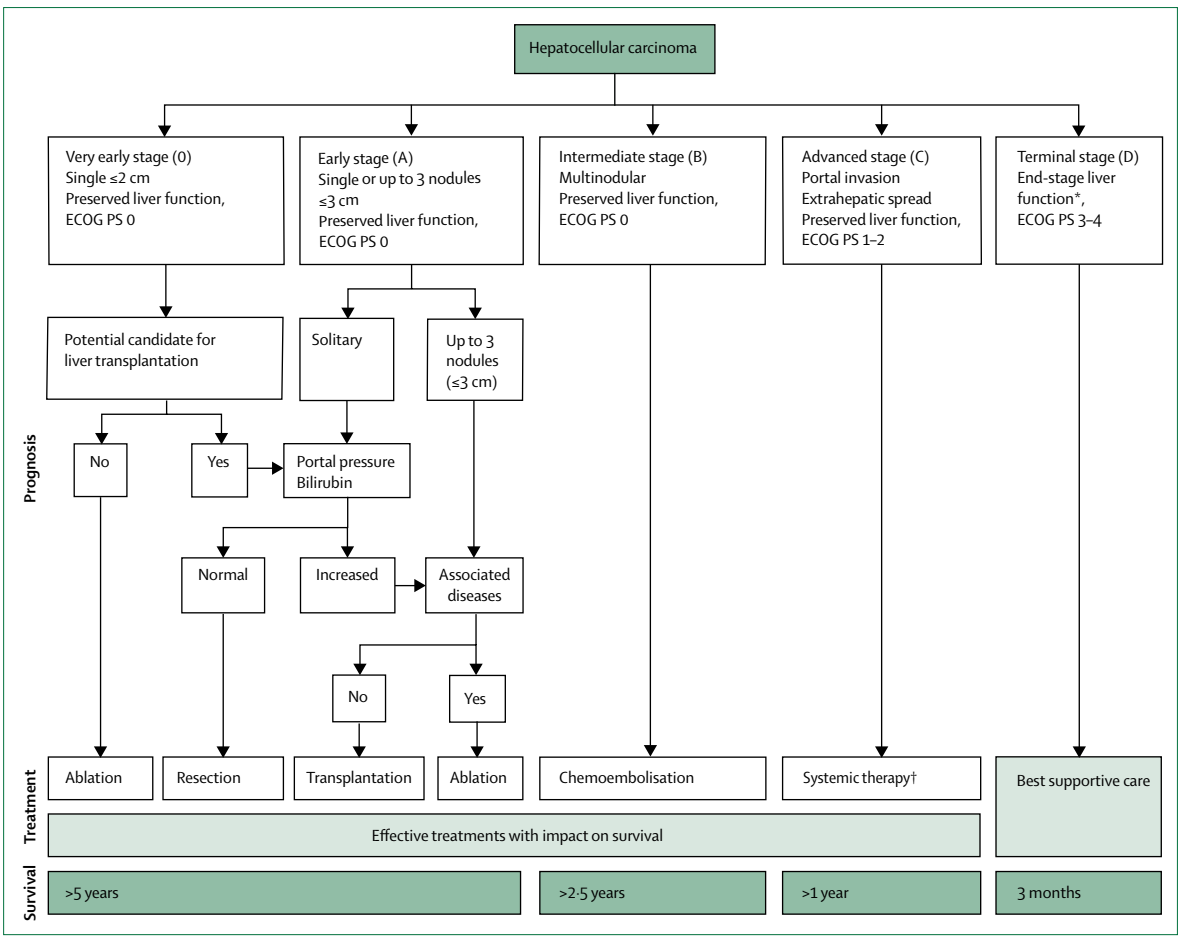

***Figure 2*: Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy**

The BCLC system establishes a prognosis in accordance with the five stages that are linked to first-line treatment recommendation. The expected outcome is expressed as median survival of each tumour stage according to the available scientific evidence. Note that liver function should be evaluated beyond the conventional Child-Pugh classification or the Model of End-stage Liver Disease (MELD) score. None of them serves to properly gauge the liver function status, and this evaluation should take into account biochemistry parameters as well as the compensated or decompensated status of the patient. Preserved liver function includes a group of patients with different degrees of liver function reserve that has to be carefully evaluated. For most treatment options, compensated liver disease (Child-Pugh stage A without ascites) is required to obtain optimal outcomes. The sole option that could be applied irrespective of liver function is liver transplantation. ECOG PS=Eastern Cooperative Oncology Group Performance Status. *Patients with end-stage cirrhosis due to heavily impaired liver function (Child-Pugh stage C or earlier stages with predictors of poor prognosis or high a MELD score) should be considered for liver transplantation. In these patients, hepatocellular carcinoma might become a contraindication if it exceeds enlistment criteria. †Currently, sorafenib followed by regorafenib has been shown to be effective. Lenvatinib has been shown to be non-inferior to sorafenib, but no second-line option after lenvatinib has been explored.

Finally, patients with end-stage disease (BCLC D) have poor liver function or marked cancer-related symptoms (ECOG Performance Status >2). These patients are not candidates for transplantation because they have a poor prognosis and instead require supportive care.

The BCLC system can be further refined. Liver function has typically been assessed using the Child-Pugh classification, which is known to have little prediction power because events that could indicate end-stage liver disease for which transplantation is necessary (eg, renal failure, spontaneous bacterial peritonitis, hyponatraemia, recurrent encephalopathy, and malnutrition) are not fully captured. If transplantation is not feasible, hepatocellular carcinoma should be categorised as terminal (stage D) and supportive care should be offered.[67] The albumin–bilirubin (ALBI) score has been shown to stratify patients across BCLC stages,[68] but its role in clinical decision making or stratification in research trials is not defined. The parameters included in the ALBI score are already used in the conventional evaluation of patients and hence, although statistically significant, it might be clinically irrelevant for decision making.[69] An increased concentration of α-fetoprotein is associated with poorer prognosis, but no robust data exist to define a cutoff value at which the treatment decision should be modified, with the potential exception of liver transplantation. Other tumour markers such as vascular endothelial growth factor, angiopoietin 2, or KIT might refine prognostic prediction in statistical modelling, but cannot yet be incorporated in the individual assessment of a specific patient. Other

	Study design	Endpoints	Benefit
Surgical treatments			
Surgical resection	Non-population based, consecutive case series	Survival	Increases survival
Adjuvant therapies	Randomised controlled trial, meta-analysis	Survival, cause-specific mortality, quality of life, or indirect surrogates including disease-free survival, progression-free survival, or tumour response	Controversial
Sorafenib in adjuvancy	Randomised controlled trial	Indirect surrogates including disease-free survival, progression-free survival, or tumour response	No increase in disease-free survival
Liver transplantation	Non-population based, consecutive case series	Survival	Increases survival
Adjuvant therapies	Non-population based, non-consecutive case series	Indirect surrogates including disease-free survival, progression-free survival, or tumour response	Treatment response
Locoregional treatments			
Percutaneous treatment	Non-population based, consecutive case series	Survival	Increases survival
Radiofrequency	Non-blinded, randomised controlled trial, meta-analysis	Survival	Increases survival
Other modalities	Non-randomised controlled trials	Indirect surrogates including disease-free survival, progression-free survival, or tumour response	Treatment response
Combined modalities	Non-population based, consecutive case series	Indirect surrogates including disease-free survival, progression-free survival, or tumour response	Treatment response
Chemoembolisation	Non-blinded, randomised controlled trial, meta-analysis	Survival	Increases survival
Internal radiation (^{131}I or ^{90}Y)	Non-blinded, randomised controlled trial	Survival	Treatment response
Systemic treatments			
Sorafenib (first line)	Double-blinded, randomised controlled trial, meta-analysis	Survival	Increases survival
Lenvatinib (first line)	Open-label, randomised controlled trial	Survival	Non-inferior to sorafenib
Regorafenib (second line)	Double-blinded, randomised controlled trial	Survival	Increases survival
Hormonal compounds (tamoxifen, antiandrogens, and seocalcitiol)	Double-blinded, randomised controlled trial, meta-analysis	Survival	No survival benefits
Systemic chemotherapy	Double-blinded, randomised controlled trial, meta-analysis	Survival	No survival benefits

Evidence-based classification adapted from the US National Cancer Institute.

Table 1: **Evidence-based benefits of treatments according to the strength of study design**

For the **US National Cancer Institute** see https://www.cancer.gov

staging systems such as the Hong Kong Liver Cancer staging system have recently been proposed to replace BCLC. The Hong Kong Liver Cancer staging system stratifies patients into nine strata according to outcome and treatment to be applied as derived from statistical modelling and personal insight.[65] Ultimately, this system would link staging with therapy, but its validation has been based on a reduction into five stages, when the link with treatment is no longer in place. Thus, its value is not established. Finally, although any system can be further refined, none will replace the expert assessment of patients' condition and effectiveness of the proposed treatment.

Treatment

The aim of treatment is to increase survival while maintaining the highest quality of life. Very frequently, the treatment decision pivots around what can be done, rather than what is worth being done. For that reason, it is paramount to evaluate the strength of scientific evidence of any treatment approach for selecting the most appropriate option for each patient at each tumour stage. Furthermore, achievement of the best therapeutic effectiveness requires the careful selection of candidates for each treatment option and the expert application of these treatments. Given the complexity of the disease and the large number of potentially useful treatments, patients diagnosed with hepatocellular carcinoma should be referred to multidisciplinary teams involving hepatologists, surgeons, radiologists (including interventional radiologists), pathologists, and oncologists. The level of evidence for most of the therapeutic options in hepatocellular carcinoma is limited to cohort investigations with few randomised controlled trials, most of which have only investigated treatment of advanced disease (table 1).

Surgical resection, transplantation, ablation, transarterial chemoembolisation,[70–72] and the tyrosine-kinase inhibitors sorafenib,[73,74] lenvatinib,[75] and regorafenib[76] are treatments with proven survival benefit. Arterial embolisation without chemotherapy,[70] external radiotherapy,[77] and radioembolisation have shown antitumour activity,[78–80] but no definitive proof of survival benefit has been found.[81,82] Systemic chemotherapy has marginal activity with associated toxicity and no survival benefit.[83] Agents such as tamoxifen, octreotide, and antiandrogens[72] are completely ineffective. Treatment indication should be evaluated individually and, if patients are not candidates for first-line therapy as per stage, the next most suitable option within the same stage or the treatment for a more advanced-stage tumour (treatment stage migration) should be considered (figure 3).

Resection

Hepatic resection is the treatment of choice for hepatocellular carcinoma in patients without cirrhosis, in whom major resections could be done without life-threatening complications. In patients with decompensated cirrhosis, hepatic resection is formally contraindicated and liver transplantation should be considered. Patients with compensated cirrhosis should be carefully evaluated to avoid treatment-related complications and achieve long-term survival. Japanese groups use the indocyanine green retention rate to identify appropriate candidates,[84] whereas portal pressure and bilirubin are the variables used in Europe and the USA.[38] Clinically significant portal hypertension (CSPH) is defined as the presence of an hepatic vein pressure gradient of more than 10 mm Hg.[85] The presence of oesophageal varices or ascites confirms the presence of CSPH. However, splenomegaly associated with a platelet count lower than 100×10^9 cells per L is not sufficient for identification of CSPH.[86] Liver stiffness measured by transient elastography can identify CSPH[87,88] and predict outcome.[88] Compared with absence of CSPH, the presence of CSPH increases the risk of 3-year and 5-year mortality (5-year mortality odds ratio [OR] 2·07, 95% CI 1·51–2·84) and also increases the risk of postoperative clinical decompensation (OR 3·04, 95% CI 2·02–4·59).[89] Patients without CSPH and normal bilirubin achieve 70% survival at 5 years, whereas survival is 50% or less when both adverse factors are present.[90] Most groups restrict the indication for resection to patients with a single tumour, as multifocality is associated with a higher recurrence rate and impaired survival.[90] Although multifocality might not be taken as a contraindication, a careful evaluation to estimate survival expectancy (and associated risks) that might be offered by other options, such as transplantation, ablation,[91,92] or chemoembolisation,[93–95] is mandatory. Tumour size is not a clear-cut limiting factor, but the risk of vascular invasion and dissemination increases with diameter.[96] An alternative treatment option is laparoscopic surgery, which is a less invasive procedure with similar long-term survival and less perioperative morbidity compared with open resection.[97] Malignant vascular invasion should be considered as a contraindication for resection. With the application of these criteria, the proportion of surgical candidates is 5–10%.

Unfortunately, tumour recurrence, including true recurrence due to dissemination and de novo tumours within the oncogenic liver, complicates 70% of cases at 5 years.[98] Late recurrence (no robust definition exists of the cutoff time) is commonly suggested to represent de novo hepatocellular carcinoma, but no validation of this concept is available. Indeed, some late extrahepatic recurrences indicate that the time definition is not valid. There is no accepted neoadjuvant or adjuvant option to reduce the risk of recurrence. Systemic chemotherapy and chemoembolisation have no efficacy, whereas retinoids, vitamin K2, transarterial ^{131}I-lipiodol, and interferon have produced promising results, but never been fully proven to be beneficial.[99] Adjuvant immunotherapy with

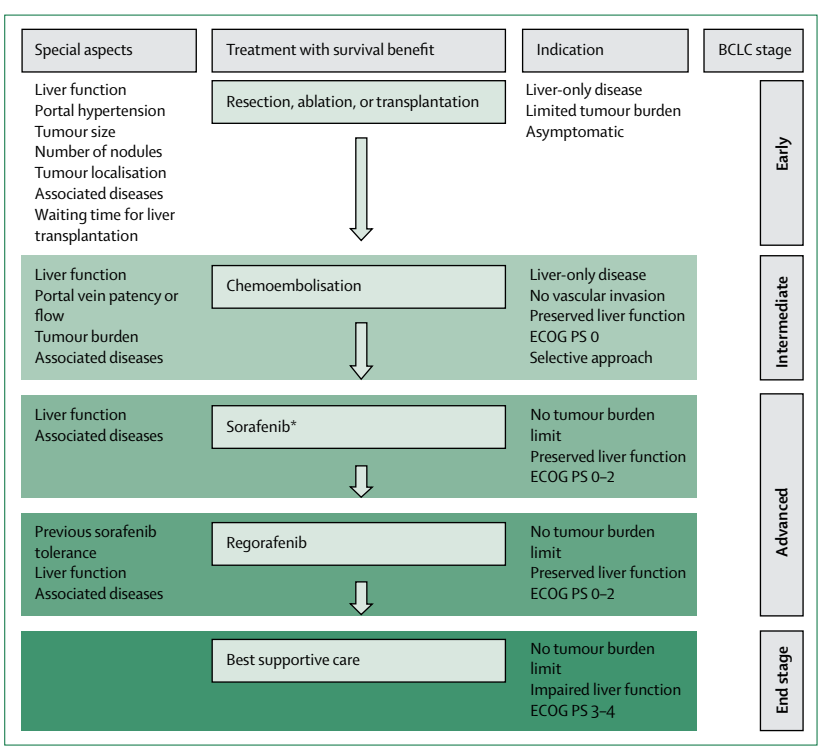

Figure 3: **Sequential treatment approach for hepatocellular carcinoma**
This figure exemplifies the difficulties in the management of hepatocellular carcinoma in clinical practice. Each tumour stage is categorised by parameters regarding tumour burden, degree of liver function impairment, and presence of cancer-related symptoms, as defined in the Barcelona Clinic Liver Cancer (BCLC) staging system. Specific aspects have not been fully registered in any staging system that help to refine the prognostic assessment and to select the best treatment option in each stage according to the available scientific evidence. This figure also illustrates the concept of treatment stage migration: if the recommended option is not feasible because of an individual patient's condition or if there is untreatable progression (defined as tumour progression associated with a clinical profile that prevents retreatment), the next most suitable option within the same stage or the treatment for a more advanced-stage tumour should be considered. Accordingly, patients in early stages might benefit from transarterial chemoembolisation, intermediate patients might benefit from sorafenib, and some patients in advanced stages with contraindications for sorafenib could enter research trials to assess new agents. ECOG PS=Eastern Cooperative Oncology Group Performance Status. *Lenvatinib has been shown to be non-inferior to sorafenib, but no second-line option after lenvatinib has been explored.

autologous cytokine-induced killer cells was shown to increase recurrence-free and overall survival after curative treatment in a multicentre, randomised, open-label, phase 3 trial that awaits validation but indicates the potential of immunotherapy in hepatocellular carcinoma.[100] Recently, sorafenib failed to prevent tumour recurrence after successful hepatic resection and ablation in early-stage hepatocellular carcinoma.[101] The most effective treatment to prevent intrahepatic recurrence is liver transplantation. The presence of microvascular invasion or satellites is associated with a high risk of recurrence, and such a profile might prime the indication of liver transplantation in patients before recurrence detection. This strategy (ab initio indication) allows some patients to be effectively treated by resection with avoidance of transplantation and, at the same time, permits an optimal use of the limited number of organs since only those patients who are likely to benefit from the treatment and have an excellent long-term outcome undergo transplantation.[102]

Liver transplantation

Theoretically, liver transplantation is the best treatment option since it might simultaneously cure the tumour and the underlying cirrhosis. The likelihood of patient survival after transplantation remains the essential criterion to indicate this treatment for hepatocellular carcinoma. The Milan criteria (a single nodule ≤5 cm or up to three nodules ≤3 cm) are the benchmark to offer the best post-liver transplantation survival in hepatocellular carcinoma (>70% 5-year survival with a recurrence rate of <10–15%).[103] These restricted criteria have become the accepted selection criteria in the USA and Europe.[104] Outcomes after liver transplantation can be predicted as a continuous function based on different combinations of tumour size and number.[105] All assessments of expansion of tumour burden show that exceeding Milan criteria is associated with increased prevalence of parameters linked to augmented risk of recurrence (microscopic vascular invasion or satellites) and thus impaired long-term outcome.[105–107] In addition, most analyses are based on the tumour burden data in the explanted liver and not on imaging findings.[105] The α-fetoprotein level and the use of total tumour volume rather than tumour size and number have been reported to improve the predictive value within and beyond Milan criteria.[108,109] A novel approach that combines tumour stage and efficacy of alternative treatment has been suggested. This model relies on the finding that post-liver transplantation survival outcomes of patients with hepatocellular carcinoma beyond Milan criteria with sustained response to pre-liver transplantation therapy are not significantly different from those of patients who meet conventional criteria.[110] Furthermore, indication of liver transplantation in hepatocellular carcinoma might be further refined according to donor availability in each allocation area, the proportion of enlisted patients without hepatocellular carcinoma versus those with hepatocellular carcinoma, and the dynamics of the waiting list.[104,110] All of these issues show the complex interaction of the several parameters that might be associated with increased recurrence risk and the challenges of designing a trial in the setting of liver transplantation.

The main limitation of liver transplantation is donor shortage. This shortage imposes a waiting time before transplantation, and during this time the tumour might progress and impede transplantation, impairing the effectiveness of the treatment when considered according to intention to treat.[104] Despite the fact that the efficacy of this treatment has not been proved, cost-effectiveness analysis supports the use of locoregional therapies when the expected waiting time exceeds 6 months, with the aim of delaying tumour progression.[104] Additionally, policies have been implemented aiming to prioritise the sickest patients, but the sole effective method to avoid waiting is to increase the number of available donors.[104] Live donation is a valid strategy with outcomes similar to those for deceased donation, but its applicability is reduced because of societal constraints and scarcity of suitable donors.

Image-guided tumour ablation

Tumour ablation is a widely accepted treatment option for patients with early-stage hepatocellular carcinoma. Ablation induces tumour necrosis by temperature modification (radiofrequency, microwave, laser, or cryo-ablation) or injection of chemical agents (most frequently ethanol). Radiofrequency ablation is the first-line ablation technique,[111] since it provides better disease control and outcomes than percutaneous ethanol injection.[112] This difference is evident in nodules that are more than 2 cm in diameter, whereas in smaller lesions the efficacy and long-term outcomes are very similar.[112] Percutaneous ethanol injection still has a role in the treatment of hepatocellular carcinoma since radiofrequency ablation cannot be applied in proximity to the gallbladder, stomach, colon, or other viscera. In some of those cases, radiofrequency ablation with a laparoscopic approach can be an option. Microwave ablation has emerged as a promising technique, with encouraging response rates in tumours between 3 cm and 5 cm in size and in tumours adjacent to vessels and the gallbladder. It requires fewer sessions, and overall survival is non-inferior to that obtained with radiofrequency ablation.[113] In patients with Child-Pugh stage A liver disease, survival after ablation is similar to survival after surgical resection,[98] challenging resection as the first-line therapy in patients with a small solitary hepatocellular carcinoma. Several randomised controlled trials done in China have compared ablation and resection in early-stage hepatocellular carcinoma, reporting opposite results.[114–116] Concerns regarding sample size calculation, randomisation, treatment allocation, trial conduction, and the lack of external validation in the USA and Europe prevent any reliable conclusion. Ablation has almost

100% efficacy in hepatocellular carcinoma nodules that are less than 2 cm in diameter (very early stage), and survival is almost identical after resection or ablation.[117] Resection allows the identification of histological parameters that predict recurrence risk. If these findings prime the indication of liver transplantation before recurrence detection, resection should still be the first-line approach in patients who would also be appropriate for transplantation. If liver transplantation is not feasible, ablation could be considered as the first-line option for patients with very early-stage hepatocellular carcinoma, and surgery could be second line for patients in whom ablation cannot be done or fails.

Image-guided transcatheter tumour therapy

Image-guided transcatheter tumour therapies aim to induce tumour necrosis and are based on the predominantly arterial vascularisation of hepatocellular carcinoma compared with the surrounding liver parenchyma. This difference in vascularisation enables the selective intravascular delivery of drugs, embolic particles, or radioactive devices.[118] Of these therapies, the only option that has shown survival benefit is transarterial chemoembolisation,[70–72] which associates the injection of chemotherapy with blockade of the arterial blood supply. More than half of the patients achieve an objective response with this procedure, as reflected by extensive tumour necrosis,[70,71,93–95] and this objective response rate translates into improved survival.[72] The development of polyvinyl alcohol spheres that enable calibrated vessel obstruction with slow release of chemotherapy has allowed standardisation of the procedure while retaining the efficacy and reducing drug-related adverse events.[119–121] Median survival in old series was around 20 months,[70,71] but with appropriate patient selection and optimal treatment delivery the current median survival exceeds 30–40 months.[93–95] Patients with compensated liver function with asymptomatic multifocal or large hepatocellular carcinoma who are not amenable to resection are optimal candidates for transarterial chemoembolisation. Portal vein thrombosis, even if segmental, and mild cancer-related symptoms are predictors of poor tolerability and impaired outcome, and systemic therapy should be considered for patients with these findings.[118] A recent randomised controlled trial[122] comparing transarterial chemoembolisation with transarterial embolisation found no differences in terms of tumour response and overall survival, but around 45% of the patients included had advanced hepatocellular carcinoma, which resulted in a median survival of less than 20 months, limiting the value of the results.

After the initial success of transarterial chemoembolisation, vascularisation increases in treated tumours, and these tumours might need to be retreated. The decision on when transarterial chemoembolisation therapy should be interrupted is complex. Transarterial chemoembolisation should not be repeated when substantial necrosis is not achieved after two rounds of treatment or when follow-up treatment fails to induce noticeable necrosis at sites that have progressed after an initial tumour response. Additionally, transarterial chemoembolisation should not be repeated on untreatable progression: that is, tumour progression associated with a clinical profile that prevents retreatment. Definitions of untreatable progressions can include major progression—extensive liver involvement, extrahepatic metastasis, or vascular invasion—but also minor intrahepatic progression associated with impaired liver function and performance status.[118] The combination of molecular targeted therapies with antiangiogenic activity, such as sorafenib and brivanib, plus transarterial chemoembolisation has not provided benefit.[123–125]

Major emphasis has been placed on the potential efficacy of transarterial radioembolisation with ^{90}Y-labelled spheres. In cohort studies, transarterial radioembolisation showed tumour response rates between 40% and 90%, and survival was comparable to that obtained with transarterial chemoembolisation and sorafenib.[78–80] Regrettably, randomised controlled trials in advanced-stage hepatocellular carcinoma failed to demonstrate a survival benefit from transarterial radioembolisation compared with sorafenib,[81,82] and current trials are testing the benefit of transarterial radioembolisation combined with sorafenib. The observed delay in tumour progression could be useful for patients who are on the waiting list for liver transplantation but, at the same time, it might be in part due to radiation damage preventing the recognition of intrahepatic progression.

Systemic therapy

Until 2008, no effective therapy existed for patients diagnosed with advanced-stage hepatocellular carcinoma or patients who transitioned into it after other therapies failed. The knowledge of the molecular events that govern tumour initiation and progression has permitted the development of targeted therapies aimed to abrogate disrupted molecular pathways. Several agents have been tested or are under development, but the only agents that have been proven to improve survival versus placebo are sorafenib[73,74] and regorafenib.[76] Both drugs are oral multikinase inhibitors that block RAF signalling as well as vascular endothelial growth factor, platelet-derived growth factor, and KIT; the mechanism of action is not well known, but these drugs have antiproliferative and antiangiogenic effects. Sorafenib was the first systemic therapy approved in hepatocellular carcinoma as a result of two positive randomised placebo-controlled trials: one multicentre trial[73] done predominantly in Europe and the USA, and another trial[74] done in the Asia-Pacific area. Cohort studies have validated the efficacy of sorafenib in clinical practice,[126–128] and none of the agents tested against sorafenib in randomised controlled trials has improved patient outcomes.[129–132] Biomarkers such as α-fetoprotein, vascular endothelial growth factor, angiopoietin 2,

hepatocyte growth factor, or KIT might have prognostic power but have no value in modifying treatment decisions.[133] The combined analysis of the two pivotal trials has shown that aetiology does not imply a different prognosis. However, the treatment benefit from sorafenib is significantly higher in patients with hepatitis C than in those with other underlying risk factors.[134] The development of dermatological adverse events is associated with better survival in patients treated with sorafenib,[135] and the pattern of progression determines post-progression survival.[127]

Most of the promising agents evaluated in phase 3 trials[129–132,136–139] as first-line and second-line treatments for hepatocellular carcinoma failed to demonstrate survival benefit despite suggestive findings from early-stage studies (table 2). Regorafenib was the only drug that demonstrated survival benefit as a second-line treatment. It was evaluated in a phase 3 trial[76] in patients with hepatocellular carcinoma who progressed but were tolerant to sorafenib and had Child-Pugh stage A liver function and an ECOG Performance Status of 0 or 1. 573 patients were randomised (379 to regorafenib; 194 to placebo). The regorafenib group had a 37% reduction in the risk of death: the median overall survival (regorafenib *vs* placebo) was 10·6 months versus 7·8 months (hazard ratio [HR] 0·63, 95% CI 0·50–0·79; p<0·0001), and the median time to progression was 3·9 months versus 1·5 months (HR 0·41, 95% CI 0·34–0·51; p<0·0001). The most common adverse events were hand–foot skin reaction, arterial hypertension, fatigue, and diarrhoea, but treatment was discontinued in only 10% of the patients because of intolerance, indicating a good safety profile in this population.[76] Cabozantinib has also recently been announced to be effective as a second-line treatment compared with placebo.[66] However, the impact of these second-line options in clinical practice remains to be determined.

Very recently, lenvatinib, an inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor-α, RET, and KIT, has been compared with sorafenib as first-line treatment in an open-label, multicentre, non-inferiority, randomised trial.[75] 954 patients were enrolled and randomised 1:1 to lenvatinib (n=478) or sorafenib (n=476). The median survival was not significantly different between both groups (13·6 months for lenvatinib *vs* 12·3 months for sorafenib, HR 0·92, 95% CI 0·79–1·06), and the treatment-emergent adverse events were similar in both groups.[75] The impact of lenvatinib in the management of patients is unknown because its target population is the same as for sorafenib.

Future perspectives

In the past 10 years, treatment of hepatocellular carcinoma has evolved considerably. Nowadays, patients with hepatocellular carcinoma can benefit from effective options that improve their survival whatever the evolutionary stage of disease at diagnosis. However, improvement can still be made in several areas. Prevention of the acquisition of the risk factors for development of hepatocellular carcinoma is the best strategy for decreasing mortality. The high efficacy of direct acting antivirals in elimination of chronic hepatitis C virus infection is expected to have an impact on the incidence of hepatocellular carcinoma, but further information about disease evolution in the patients after viral cure needs to be collected. Promotion

	Study (year)	Randomisation	Time to progression		Survival	
			Months	p value	Months	p value
First line						
Sorafenib*	Llovet et al (2008)[73]	Sorafenib (n=299) *vs* placebo (n=303)	5·5 *vs* 2·8	<0·001	10·7 *vs* 7·9	<0·001
Sorafenib*	Cheng et al (2009)[74]	Sorafenib (n=150) *vs* placebo (n=76)	2·8 *vs* 1·4	<0·001	6·5 *vs* 4·2	0·001
Sunitinib	Cheng et al (2013)[129]	Sunitinib (n=530) *vs* sorafenib (n=544)†	3·6 *vs* 3·6	NS	7·9 *vs* 10·2	NS
Brivanib	Johnson et al (2013)[130]	Brivanib (n=577) *vs* sorafenib (n=578)	4·2 *vs* 4·1	NS	9·5 *vs* 9·9	NS
Sorafenib plus erlotinib	Zhu et al (2015)[131]	Sorafenib plus erlotinib (n=362) *vs* sorafenib (n=358)	3·2 *vs* 4·0	NS	9·5 *vs* 8·5	NS
Linifanib	Cainap et al (2015)[132]	Linifanib (n=514) *vs* sorafenib (n=521)	5·4 *vs* 4·0	0·001	9·1 *vs* 9·8	NS
Sorafenib plus doxorubicin	Abou-Alfa et al (2016)[83]	Sorafenib plus (n=173) doxorubicin *vs* sorafenib (n=173)	NA	NA	9·3 *vs* 10·5	NS
Lenvatinib*	Kudo et al (2017)[75]	Lenvatinib (n=478) *vs* sorafenib (n=476)†‡	8·9 *vs* 3·7	<0·001	13·6 *vs* 12·3	<0·001
Second line						
Regorafenib*	Bruix et al (2016)[76]	Regorafenib (n=379) *vs* placebo (n=194)	3·9 *vs* 1·5	<0·0001	10·6 *vs* 7·8	<0·0001
Brivanib	Llovet et al (2013)[136]	Brivanib (n=263) *vs* placebo (n=132)	4·2 *vs* 2·7	0·001	9·4 *vs* 8·2	NS
Everolimus	Zhu et al (2014)[137]	Everolimus (n=362) *vs* placebo (n=184)	2·9 *vs* 2·6	NS	7·6 *vs* 7·3	NS
Ramucirumab	Zhu et al (2015)[138]	Ramucirumab (n=283) *vs* placebo (n=282)	3·5 *vs* 2·6	<0·0001	9·2 *vs* 7·6	NS
Tivantinib	Rimassa et al (2017)[139]	Tivantinib (n=226) *vs* placebo (n=114)	NA	NA	8·4 *vs* 9·1	0·81

NS=non-significant. NA=not available. *Agents with survival benefit. †Open-label trial. ‡Non-inferiority design.

Table 2: **Targeted therapies evaluated in phase 3 trials in hepatocellular carcinoma**

of healthy life habits, including a decrease in alcohol abuse, and prevention of metabolic syndrome will also have an impact on the incidence of hepatocellular carcinoma. Recurrence after ablation or resection and progression after effective chemoembolisation are major drawbacks in the management of hepatocellular carcinoma, and thus effective adjuvant therapies are urgently needed. Another relevant issue is the radiological assessment of tumour response and its capacity to predict efficacy. Since the aim of locoregional therapies is achievement of complete necrosis of the lesion, the measurement of diameter changes alone is inaccurate, and incorporation of the assessment of tumour necrosis identified by the absence of contrast uptake during the arterial phase is required.[140] This was the rationale for development of the European Association for the Study of the Liver (EASL) criteria and the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria, which take into account the sum of diameters of the viable tumour.[141] The value of mRECIST in the evaluation of systemic therapy in hepatocellular carcinoma is not established. Reduced contrast uptake because of haemodynamic changes induced by treatment should not be considered as necrosis. Thus, a registered higher objective response by mRECIST has not been associated with survival improvement. In addition, the simultaneous use of RECIST 1.1 and mRECIST in the regorafenib trial[76] showed the same time to progression figures by both criteria. However, the major concern is that time to progression does not accurately correlate with overall survival, and thus it is not informative as a surrogate outcome.[136] Tumour progression is worse than stable disease, but its impact on prognosis varies according to pattern of progression. This novel concept is key in assessment of results from ongoing investigations and design of therapeutic trials on disease progression.[76,127] Novel promising treatment strategies such as immunotherapy are under investigation.[142] For example, nivolumab, a programmed cell death protein-1 (PD-1) immune checkpoint inhibitor, has shown antitumoural activity with a 15–20% rate of objective responses that are durable in time, with an appropriate safety profile. Survival data in single-arm phase 2 studies are promising,[143] but survival benefit should be confirmed in the ongoing phase 3 trial (NCT02576509).

Finally, much hope has been placed in the identification of novel targets and prognosis predictors through molecular profiling. This approach should identify new therapeutic strategies, thus enabling precision medicine. Despite the appeal of this approach, it is limited by the well known intra-nodule and inter-nodule tumour heterogeneity and heterogeneity in tumour evolution. The identification of circulating tumour products in the blood (liquid biopsy) might surpass these limitations, but this strategy is still a matter of research in liver cancer.

Contributors

AF conducted the bibliographic research, was responsible of the initial text design, initial drafting, and final writing. MR participated in the initial drafting and manuscript review. JB was responsible for the initial text design, manuscript review, and final writing. All the authors reviewed and approved the final version.

Declaration of interests

AF has received consultancy fees from Bayer and lecture fees from Bayer, Biocompatibles/BTG, and Gilead. MR has received consultancy fees from Bayer and Bristol-Myers Squibb; and lecture fees from Bayer, Biocompatibles/BTG, and Gilead. JB has received grant support and consultancy fees AbbVie, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Biocompatibles/BTG, Terumo, Novartis, Sirtex, Eisai, Arqule, Angiodynamics, Kowa Pharmaceuticals, GlaxoSmithKline, Roche, Lilly, Onxeo, and OSI Pharmaceuticals.

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