Hepatocellular carcinoma

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Hepatocellular carcinoma is one of the most common cancers worldwide and represents a major global health-care challenge. Although viral hepatitis and alcohol remain important risk factors, non-alcoholic fatty liver disease is rapidly becoming a dominant cause of hepatocellular carcinoma. A broad range of treatment options are available for patients with hepatocellular carcinoma, including liver transplantation, surgical resection, percutaneous ablation, and radiation, as well as transarterial and systemic therapies. As such, clinical decision making requires a multidisciplinary team that longitudinally adapts the individual treatment strategy according to the patient's tumour stage, liver function, and performance status. With the approval of new first-line agents and second-line agents, as well as the establishment of immune checkpoint inhibitor-based therapies as standard of care, the treatment landscape of advanced hepatocellular carcinoma is more diversified than ever. Consequently, the outlook for patients with hepatocellular carcinoma has improved. However, the optimal sequencing of drugs remains to be defined, and predictive biomarkers are urgently needed to inform treatment selection. In this Seminar, we present an update on the causes, diagnosis, molecular classification, and treatment of hepatocellular carcinoma.

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Introduction

Hepatocellular carcinoma is one of the most common malignancies and a leading cause of cancer-related mortality worldwide. In this Seminar, we discuss the epidemiology, risk factors, prognostic factors, diagnosis, and treatment (from surgery, liver transplantation, and local ablative and intra-arterial therapies to the latest developments in molecular and immune-based therapies for advanced disease) and provide perspectives for future developments.

Epidemiology and risk factors

In 2020, almost 906000 people were diagnosed with liver cancer globally, the most common form of which was hepatocellular carcinoma (figure 1).[1] Hepatocellular carcinoma is the third leading cause of cancer deaths worldwide, with a relative 5-year survival rate of approximately 18%. The similarity between incidence and mortality (830000 deaths per year) underlines the dismal prognosis associated with this disease.[2]

The diagnosis of hepatocellular carcinoma peaks in people aged between 60 and 70 years, and predominantly affects men.[3] The incidence of hepatocellular carcinoma varies by geographical region and ethnicity, which is largely attributed to the prevalence of (and the age of exposure to) major risk factors. Most patients with hepatocellular carcinoma have a background of chronic liver disease as a consequence of chronic infections with the hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol abuse or alcoholic steatohepatitis (ASH), and non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH). Obesity, diabetes, and nicotine use are also associated with increased incidence of hepatocellular carcinoma, as are rare conditions such as haemochromatosis or hereditary tyrosinaemia type 1. Additionally, rates of hepatocellular carcinoma in patients with HIV have increased, specifically in those who are co-infected with HBV or HCV.[4] Exposure to aflatoxin B1 is especially relevant in Asia, where it overlaps with HBV infection.[5] The prevalence of risk factors for hepatocellular carcinoma varies globally, with a predominance of HBV in Asia, HCV in Japan, and NAFLD and NASH and alcohol in Europe and North America. In many cases, the risks of developing hepatocellular carcinoma are multifactorial and include demographic factors (age, sex, and ethnicity), severity and activity of underlying disease (fibrosis stage, inflammatory activity, and treatment), metabolic factors (diabetes and obesity), and lifestyle factors (alcohol intake and smoking). The global incidence of viral hepatitis-related malignancies has declined since the 2000s because of the implementation of neonatal HBV vaccination programmes and the availability of highly effective antiviral treatments for HBV and HCV.[6–10] To predict the remaining risk of hepatocellular carcinoma in these patients, several scores have been established and validated that help to guide surveillance strategies, specifically for patients with liver cirrhosis.[11–13] Of note, antiviral treatment improves survival in patients with HBV-related hepatocellular carcinoma, and most likely also in HCV-related hepatocellular carcinoma. However, the long-term effect of successful anti-HCV therapy on the recurrence risk of hepatocellular carcinoma remains inconclusive.[14–17]

Although the prevalence of virally driven hepatocellular carcinoma has declined, the incidence of NAFLD and NASH-related liver cancer has increased.[18] NAFLD is part of a multisystem disease and is considered the hepatic manifestation of the metabolic syndrome,[19] although it

Search strategy and selection criteria

We searched MEDLINE and PubMed databases for all articles published in English using the terms "hepatocellular carcinoma" or "liver cancer", focusing on randomised trials and other high-quality studies from Jan, 2000, up to March, 2022. Publications within the past 5 years were prioritised, although older, relevant studies that were high quality were also selected. Meeting abstracts from peer-reviewed congresses were also included if they were deemed to be of high quality and could potentially change practice.

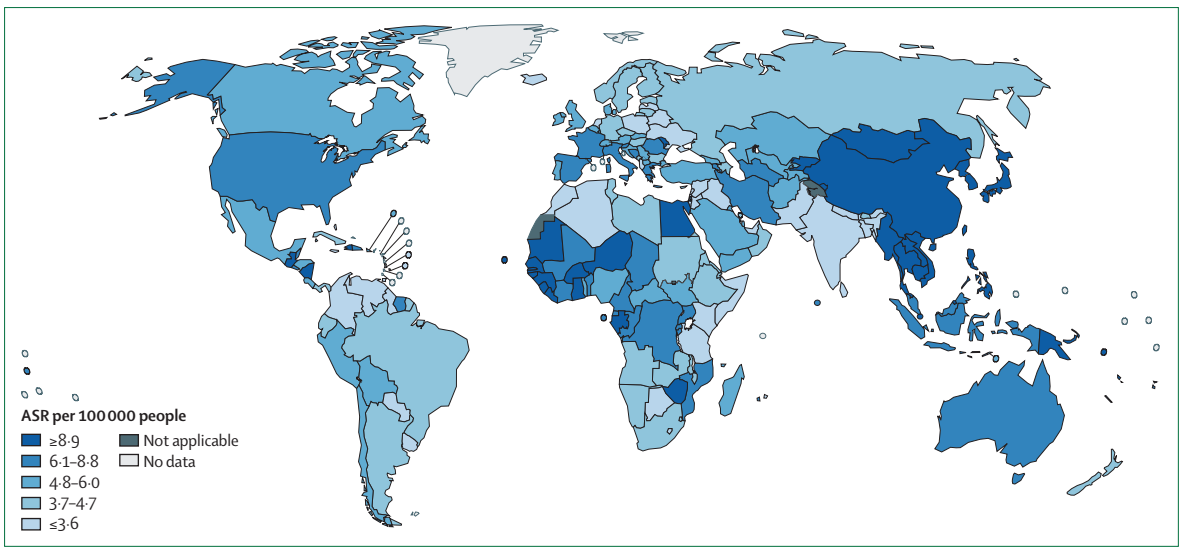

Figure 1: **ASR of liver cancer, 2020**
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For more on **Globocan** see https://gco.iarc.fr/today/home

can also occur in people who are not obese, especially in Asian people.[20] NAFLD is now the most common chronic liver disease, with a worldwide prevalence of 25% (ranging from 14% in Africa to 32% in the Middle East, and approximately 25% in Europe and the USA).[21] Of note, optimisation of both glycaemic control and bodyweight are desirable, as they appear to be independently associated with an increased risk of liver cancer.[22] 20% to 30% of NAFLD and NASH-related hepatocellular carcinomas develop in the absence of cirrhosis. However, prospective studies that define the risk of hepatocellular carcinoma in patients with NAFLD and NASH are not yet available.[23,24] Of note, variants in patatin-like phospholipase domain containing 3 (*PNPLA3*; rs738409), transmembrane 6 superfamily member 2 (*TM6SF2*; rs58542926), and hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*) are associated with the development of hepatocellular carcinoma in people with NAFLD and NASH, but also in people with alcoholic liver disease.[25,26] Alcohol consumption is a well-established risk factor for several diseases and accounts for approximately 5% of the global burden of cancer.[27] Alcohol-related liver disease is significantly more common in men, but the relative risk of developing hepatocellular carcinoma is higher in women compared with men.[28,29] Coffee has been consistently associated with a decreased risk of liver cancer. A meta-analysis published in 2017 showed that two cups of coffee per day could reduce risk of hepatocellular carcinoma by 35%,[30] but the mechanisms underlying the protective effects of coffee were not clear.

Prevention and screening

Chronic liver disease predisposes people to hepatocellular carcinoma. The prevention of chronic liver disease, therefore, reduces the population at risk. The effect of this approach has been clearly shown in Taiwan, where the introduction of a national HBV vaccination programme for newborn babies in 1984 resulted in a 35·9% reduction in the incidence of hepatocellular carcinoma in those younger than 30 years.[31] Although no equivalent vaccination for HCV is available, the advent of direct-acting antivirals offers the prospect of eliminating HCV in line with the aims of the global health sector strategy for viral hepatitis.[32] Meanwhile, ASH, NAFLD, and NASH are emerging as dominant risk factors, and public health measures are urgently needed to react to this epidemiological transition. There are, however, only few data to support the efficacy of hepatocellular carcinoma surveillance in these patients.

In those with established liver disease, chemopreventive measures that show promise include low dose aspirin,[33] statins,[34–36] and metformin.[37,38] In addition to preventing disease, early detection remains key to improving outcomes. The only randomised trial was conducted in China and there are not yet any robust data supporting the general application of screening.[39] Nevertheless, international guidelines recommend surveillance of populations at high risk with six-monthly abdominal ultrasound with or without alpha fetoprotein (AFP).[40,41] However, controversies exist regarding the value of AFP. Although some studies suggest that AFP is the best single biomarker for hepatocellular carcinoma and complements the use of ultrasound, others have questioned the sensitivity, specificity, and predictive value of AFP testing.[42] At a cutoff value of 20 ng/mL, AFP was found to have a sensitivity between 49% and 71% and a specificity between 49% and 86% in detecting hepatocellular carcinomas smaller than 5 cm.[43] In addition to a better implementation of surveillance for patients at risk, novel surveillance tests are needed,[44] particularly for the increasing number of

patients with NAFLD, for whom ultrasound performance is frequently impaired in the setting of obesity.[45] Although there is little evidence to support screening of subgroups, it should be applied in those for whom the incidence of hepatocellular carcinoma makes it cost-effective and in those for whom a competing risk of death would not prevent the benefit of early detection. This scenario is particularly relevant for patients with NAFLD and NASH without cirrhosis, for whom the incidence of hepatocellular carcinoma is low but the competing risk of death from diabetes or ischaemic heart disease is high.

Diagnosis

Hepatocellular carcinoma can be diagnosed on the basis of validated imaging criteria (in people who have liver cirrhosis) or tissue biopsy. Commonly used imaging modalities include multiphasic CT or MRI, in which hepatocellular carcinoma typically shows enhancement (brightness compared with surrounding parenchyma) in the early arterial phase, and washout (temporal decrease in enhancement relative to surrounding parenchyma) in the delayed phase. The latter creates a peripheral rim of enhancement around the tumour, resulting in the formation of a capsule; an observation highly specific for hepatocellular carcinoma.[46] This imaging feature has been prospectively confirmed and universally adopted by guidelines.[40,41,46]

Usually, solid hepatic nodules raise suspicion for hepatocellular carcinoma once they are ≥1 cm, especially in patients with liver cirrhosis. Lesions that are identified incidentally or through regular screening by ultrasound, dynamic contrast-enhanced CT or MRI of the abdomen should be obtained for further assessment. As not all tumours present with classic enhancement patterns, the liver imaging reporting and data system (LI-RADS, LR) was developed to help guide the diagnosis of hepatocellular carcinoma in patients at high risk without the need for tissue biopsy. LI-RADS is based on tumour size, contrast dynamics, capsule appearance, and threshold growth, and categorises nodules into the following categories: LI-RADS non-categorisable due to inadequate imaging; LR-1: definitely benign; LR-2: probably benign; LR-3: intermediate risk of hepatocellular carcinoma (confidence risk 12–50%); LR-4: probably hepatocellular carcinoma (47–80%); LR-5: definitely hepatocellular carcinoma (93–96%), and LR-M: a probably malignant lesion but not definitely hepatocellular carcinoma.[47]

Pathological diagnosis of hepatocellular carcinoma is typically based on the examination of a resection or explant specimen, or from a biopsy sample. Historically, biopsy has been reserved for lesions in which non-invasive imaging criteria for diagnosis are not met or are not applicable (for patients without cirrhosis). Especially in the setting of advanced disease, biopsy is now increasingly done because diagnostic certainty is needed to ensure appropriate use of systemic therapy. The routine application of biopsy in advanced disease has been shown to be safe and overcomes the limitations of non-invasive criteria.[48] Of note, a prospective multicentre audit evaluated biopsy in the setting of advanced disease and showed that the positive predictive value of non-invasive criteria for diagnosis of hepatocellular carcinoma is 91·4%. This finding shows that up to 9% of patients would receive inappropriate therapy in the absence of a biopsy.[48]

The histological classification and criteria for diagnosis of hepatocellular carcinoma have been defined by WHO and the International Consensus Group for Hepatocellular Neoplasia.[49,50] In resection and explant specimens, pathological staging is done according to the TNM classification and grade is typically defined as well, moderate, or poor.[51] Within a cirrhotic liver, the differentiation of hepatocellular carcinoma from a dysplastic nodule is supported by the presence of architectural and cellular atypia (trabecular disarray and an increased nuclear to cytoplasmic ratio), and the presence of stromal or vascular invasion. Diagnosis is further supported by immunohistochemistry for markers including glypican 3, heat shock protein 70, and glutamine synthetase. The presence of two or more of these markers increases the diagnostic specificity to 100%.[52,53] In the non-cirrhotic liver, well differentiated tumours need to be distinguished from hepatocellular adenomas. Less well differentiated tumours might need to be distinguished from other liver tumours by evidence of hepatocellular differentiation markers (eg, arginase). The morphology of hepatocellular carcinoma has been associated with specific molecular alterations. For instance, the histological subtype macrotrabecular-massive, observed in 12% of early hepatocellular carcinomas, has an aggressive phenotype with high levels of AFP and specific molecular features (ie, G3 transcriptomic subgroup, *TP53* mutations, and *FGF19* amplifications).[54] Tumours that display both hepatocytic and cholangiocytic differentiation represent a distinct entity, termed combined hepatocellular carcinoma-cholangiocarcinoma. Combined hepatocellular carcinoma-cholangiocarcinoma represents fewer than 5% of primary liver tumours and evidence suggests that this entity is associated with a worse prognosis than hepatocellular carcinoma.[55] Particular subtypes of hepatocellular carcinoma can be distinguished by pathological features, and the presence of a specific fusion transcript (DNAJB1-PRKACA) is pathognomonic for fibrolamellar hepatocellular carcinoma.

Clinical and biochemical biomarkers in hepatocellular carcinoma

To improve outcomes in hepatocellular carcinoma, it will be essential to decipher how key clinical and molecular characteristics influence disease course and treatment response. The prognosis for hepatocellular carcinoma depends not only on tumour characteristics, such as tumour burden, extrahepatic spread, vascular infiltration, or tumour differentiation, but is heavily influenced by

the underlying liver disease. Additionally, higher levels of serum AFP are significantly associated with increased mortality, independent of demographic and clinical factors or treatment, and have been shown to predict the risk of tumour recurrence after resection and liver transplantation.[56–60]

Several models and scores have been developed to evaluate the hepatic functional reserve as an independent prognostic factor for survival in patients with hepatocellular carcinoma. The Child-Pugh score, which is based on clinical and laboratory parameters, was initially conceived to assess prognosis in patients with portal hypertension undergoing surgery for variceal bleeding and is now broadly used to evaluate liver function in clinical practice. The albumin-and-bilirubin (ALBI) grading system, introduced in 2015, is based only on serum albumin and bilirubin, and consequently facilitates a more objective assessment of liver function compared with the Child-Pugh system.[61] Post-hoc analyses of several phase 3 trials have confirmed the strong prognostic role of liver function during systemic therapy in advanced hepatocellular carcinoma.[62–64]

Apart from prognostic biomarkers, predictive biomarkers to guide treatment decisions are urgently needed. Efforts in biomarker discovery must consider the substantial transcriptional and genetic heterogeneity of hepatocellular carcinoma. Several molecular signatures have been published that converge on at least two major pathway classifications: the proliferation class, characterised by chromosomal instability, and the non-proliferation class, which is associated with a better prognosis.[65–67] Although these molecular classifications (which combine transcriptomic analyses, somatic genetic alterations, and clinical and biological features) define the inter-patient hepatocellular carcinoma heterogeneity and link molecular characteristics to disease causes,[68,69] their use in clinical practice is limited and the predictive power of any of the proposed signatures has not yet been established in prospective trials.[70] With regards to atezolizumab plus bevacizumab as the current standard of care in patients with advanced hepatocellular carcinoma, a post-hoc analysis of the pivotal IMbrave150 phase 3 trial identified molecular correlates, including gene signatures for T-cell subsets and for myeloid inflammation that were positively associated with clinical outcome.[71]

See Online for appendix

Patients with hepatocellular carcinoma typically have a low to moderate tumour mutational burden, with an average of 2·9 mutations per megabase, corresponding to approximately 40 to 60 somatic coding mutations.[72] Recurrent genetic alterations include TERT promoter (50–60%), *TP53* (20–40%), *CTNNB1* (15–40%), and *ARID1A* mutations (10–20%), for which no targeted therapies are yet available.[68] As an emerging diagnostic approach, liquid biopsy, which encompasses the analysis of circulating tumour cells, cell free DNA, or exosomes, has the potential to complement and even substitute for tissue analysis. The key advantage of liquid-based diagnostics is the ability to conduct non-invasive, longitudinal sampling.[73–75] Initial data show that the presence and abundance of circulating tumour cells can predict disease prognosis and response to therapy in patients with hepatocellular carcinoma,[76] but their use in clinical management needs to be validated in prospective cohorts. In addition, high serum levels of several angiogenesis biomarkers (eg, VEGF A and ANG-2) have been associated with poor prognosis in hepatocellular carcinoma,[77] but none of these markers is able to predict response to treatment, specifically for the currently used multi-target tyrosine kinase inhibitors (TKIs).[78–82] Finally, several inflammatory markers, including the neutrophil-to-lymphocyte ratio and the C-reactive protein-based and AFP-based CRAFITY score, might be of interest in respect to the rapidly evolving field of immuno-oncology. Moreover, these markers might not only predict survival, but also identify patients who will have a greater overall survival benefit under systemic therapy.[83–86]

Treatment

Treatment options for patients with hepatocellular carcinoma are outlined in national and international guidelines, with slight differences in the therapeutic approach between Asia, Europe, and North America.[87–91] The Barcelona Clinic of Liver Cancer (BCLC) algorithm is the most widely used staging system and subdivides patients with hepatocellular carcinoma into five clinical stages: very early stage (BCLC 0), early stage (BCLC A), intermediate stage (BCLC B), advanced stage (BCLC C), and terminal stage (BCLC D).[92]

Surgery

Surgery (liver resection or liver transplantation) represents the main curative treatment option for patients with hepatocellular carcinoma. Ideal candidates for liver surgery are those with single tumours and maintained liver function. Liver transplantation is generally recommended for patients with multifocal disease or decompensated cirrhosis (appendix p 1). The surgical management of patients with hepatocellular carcinoma who have cirrhosis is complex. Patients should therefore be assessed by multidisciplinary teams in experienced centres and both resection and transplantation should be considered.

When treating a patient with hepatocellular carcinoma with liver resection it is important to determine the patient's underlying liver function. Hepatocellular carcinoma in non-cirrhotic liver is less common but, in this population, liver resection should be the first treatment option if the tumour is technically resectable.[93,94] The goal of liver resection in patients with hepatocellular carcinoma is to achieve a complete R0 outcome, with clear resection margins. However, given that most patients with hepatocellular carcinoma will have underlying liver disease, liver resection should also aim to preserve as much parenchyma as possible to decrease the risk of liver

decompensation. Several refinements in surgical techniques have been made to achieve minimal morbidity and mortality after liver resection. Minimally invasive techniques have also been developed for liver surgery and represent the first option for resection of hepatocellular carcinoma in most centres worldwide due to equivalent oncological results to open surgery and better short-term outcomes.[95,96] Classically, liver resection has been recommended to patients with compensated liver cirrhosis without portal hypertension. Indirect evidence of portal hypertension is based on the presence of varices and enlarged spleen and low platelet count (<100 000 per µl). In patients that have direct measurements taken, those with a hepatic venous pressure gradient over 10 mm Hg are generally not considered for surgical resection because of the greater risk of poor outcomes.[97] However, with advancements in minimally invasive techniques, some patients with portal hypertension could benefit from liver resection with minimal risk of liver decompensation.[98,99] Pre-surgical liver function can be evaluated by model for end-stage liver disease score or ALBI score, indocyanine green clearance, or by ultrasound-based assessment of liver stiffness.[100–103] Several risk factors for poor outcome have been identified and are related to multifocality, satellitosis, and the presence of vascular invasion.[104]

There is still debate on the best type of resection, and comparisons between anatomical and non-anatomical resections in hepatocellular carcinoma have produced discrepant results.[105,106] Theoretically, anatomical liver resections should improve clinical outcomes due to the risk of satellite lesion distribution through the anatomical pedicle. Although the 5-year overall survival following surgical resection is around 70%,[107] a main drawback of resection is the high incidence of tumour recurrence in the liver, which occurs in up to 80% of patients. Concerning adjuvant treatment, evidence from the STORM trial[108] did not show a benefit of sorafenib over placebo, and no adjuvant therapy can yet be recommended. Ongoing trials aim to address the efficacy of immunotherapy as adjuvant or neo-adjuvant treatment, with initial promising results from phase 2 trials.[109–111]

Liver transplantation

A post-transplantation 5-year survival rate of 75–80%, with low risk of recurrence (approximately 15%), can be achieved in patients with hepatocellular carcinoma undergoing liver transplantation. The reason behind these superior outcomes is that liver transplantation treats both the hepatocellular carcinoma with the widest surgical margins as well as the underlying liver cirrhosis, which is a key risk factor for tumour recurrence. The main limitation for liver transplantation is the shortage of available organs for all patients in need and, therefore, efforts have been made to select patients with the best outcomes from liver transplantation. The selection of patients for liver transplantation is frequently based on criteria that strictly take the size and the number of tumours into account. However, several studies have shown that these parameters alone might not be the best predictors of outcomes, and therefore other biological markers and surrogates of tumour biology are increasingly being used to select patients for liver transplantation (appendix pp 1–2).

Owing to the imbalance between patients in need of liver transplantation and the availability of organs, patients with hepatocellular carcinoma are required to wait between 6 and 9 months in many jurisdictions around the world until they receive a liver transplant. To avoid tumour progression, patients are treated while waiting for transplantation, which is referred to as bridging therapy. Individual patients might also receive treatment to reduce tumour mass to fulfil a particular criterion for transplantation, which is known as downsizing or downstaging.[112] The most commonly applied bridging modality is transarterial chemoembolisation (TACE), but ablation and radiation are also used. In this context, living donor liver transplantation has emerged as a good option for patients with hepatocellular carcinoma and is, in experienced centres, associated with superior outcomes compared with liver transplantation from deceased donors when outcomes are assessed from the time of listing.[113,114] This result is due to a decrease in drop-out. However, a note of caution should be made when using living donors in this context to avoid fast-tracking patients with a recent hepatocellular carcinoma diagnosis to transplantation.

Ablation

Thermal ablation is recommended for patients with early-stage hepatocellular carcinoma (≤2 cm), as well as for patients with 2–4 cm lesions that are not suitable for surgical resection because of anatomical reasons or patient conditions. Radiofrequency ablation (RFA) is the most commonly used ablation technique for the treatment of hepatocellular carcinoma. The technique entails inducing thermal injury to the tumour tissue through electromagnetic energy deposition. By applying the RFA probe to the tumour, a closed-loop circuit is formed through which alternating electric fields pass. This process results in a high level of heat with ultimate damage to the target tissue. To achieve necrosis, a temperature of 50–100°C should be maintained to the entire tumour volume for 4–6 min.[115] With contemporary data, local ablation is now considered a potentially curative therapy for small hepatocellular carcinomas (<3 cm),[116,117] and most guidelines recommend RFA as first-line therapy for single tumours smaller than 2 cm.[40,118,119] In these patients, response rates of 70–90% can be achieved after 1–2 treatment sessions (appendix p 4). Superior outcomes have been shown in patients with at least a 1 cm margin. Multiple studies have compared the effectiveness of RFA to surgical resection. One trial that compared no touch multibipolar RFA to surgical resection in solitary hepatocellular carcinoma

(2–5 cm) showed similar overall survival for both methods, despite the higher rates of recurrence in the cohort that received ablation.[120] Microwave ablation (MWA) was originally developed to help achieve intraoperative haemostasis. The advantages of MWA over RFA, including higher ablative temperatures, shorter interventional times, and overcoming the heat sink effect (the cooling effect due to flowing blood that leads to a smaller ablation volume), have resulted in MWA overtaking RFA as the preferred ablation technique in early-stage hepatocellular carcinoma.[121] In a phase 2 trial[122] of 152 patients, no differences between RFA and MWA were observed in terms of local tumour progression at 2 years. Other hepatic ablation techniques, including cryoablation and irreversible electroporation, are still under investigation. Emerging data for cryoablation show similar outcomes to RFA in hepatocellular carcinoma tumours smaller than 4 cm.[123] However, a study that used propensity score matching showed a survival benefit in patients treated with RFA compared with cryoablation.[124] There have been some recent trends combining local ablation with other locoregional therapies (eg, TACE-RFA), as well as radiotherapies and immunotherapies (appendix p 4). One study that added iodine-125 to RFA was found to significantly lower recurrence of hepatocellular carcinoma and improve overall survival.[125] However, overall, these data were largely premature, with further investigations needed, and there are no guidelines that recommend ablation with systemic therapies outside of a clinical trial.

Intra-arterial therapies

As hepatocellular carcinoma tumours are hypervascular and derive most of their blood supply from the hepatic artery, intra-arterial therapy represents a mainstay of treatment for intermediate stage hepatocellular carcinoma. Intra-arterial therapy involves the direct intra-arterial injection of particles (with or without chemotherapeutic agents) within the tumour vascularity. In general, intra-arterial therapy is categorised into bland particle embolisation (TAE), chemoembolisation (conventional trans-arterial chemoembolisation [cTACE] or drug-eluting bead [DEB]-TACE), or radioembolisation. In all cases, the hepatic artery is accessed with microcatheters via groin access. Depending on the treatment, overnight hospitalisation might be necessary to manage post-embolisation syndrome for TAE and TACE.

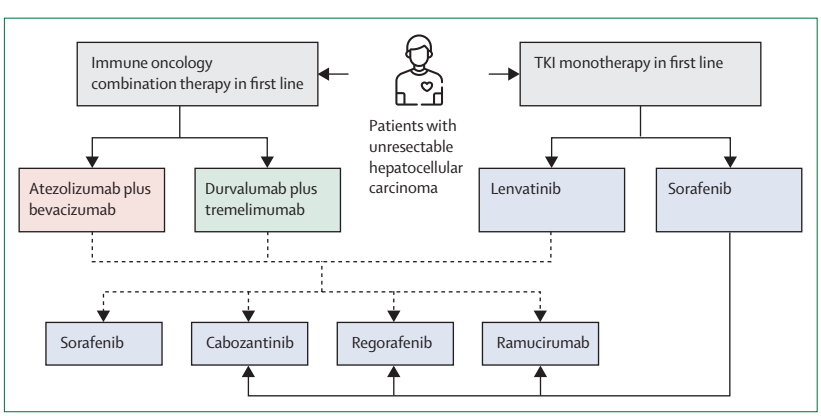

Figure 2: **Systemic therapy options for patients with hepatocellular carcinoma**
Dashed lines represent treatment sequences that are recommended without phase 3 evidence. Cabozantinib, regorafenib, and ramucirumab have been evaluated after first-line treatment with sorafenib. TKI=tyrosine kinase inhibitor.

TAE involves the injection of 100–500 micron-sized particles until stasis is reached. The rationale for this approach involves the arterial dependence of hepatocellular carcinoma tumours, with subsequent hypoxia and necrosis. The seminal TACE study[126] from 2002, which randomly assigned patients to receive cTACE, TAE, or placebo, was stopped when it was shown that cTACE had survival benefits compared with placebo. Although TAE also showed survival benefits, the study was stopped before reaching significance. Hence, no conclusion could be made about TAE in this study. Since the publication of this study, cTACE has been considered the international standard of care for intermediate stage disease, with survival rates ranging from 20 months to 36 months (appendix p 4). This procedure has been markedly improved using the principles of selectivity during injection, minimising the risk of non-target embolisation and liver decompensation. In an attempt to better standardise drug delivery and decrease post-embolisation syndrome, DEB-TACE was developed to ensure more constant and tumour-specific drug delivery. In 2010, PRECISION V,[127] an international, randomised phase 2 study that compared cTACE and DEB-TACE was published. Although the study did not meet its primary endpoint of improving objective response rate, DEB-TACE was associated with significantly fewer side-effects than cTACE that were related to the leakage of doxorubicin into the systemic circulation. Two randomised trials did not show any benefit of cTACE or DEB-TACE over TAE.[128,129] Despite these results, cTACE remains the most widely used intra-arterial therapy for intermediate stage hepatocellular carcinoma.

The technical approach for radioembolisation is identical to other intra-arterial therapies, whereby hepatic arterial access is obtained and a therapeutic is injected. Although the mechanism of action for traditional intra-aterial therapy includes ischaemia (with or without a chemotherapeutic), radioembolisation relies on the delivery of 40 micron-sized radiation particles without ischaemia or alteration in hepatic arterial blood flow. The persistence of hepatic arterial flow results in the near-elimination of post-embolisation syndrome. With fatigue being the most prominent symptom of post-radioembolisation syndrome, this treatment can be given on an outpatient basis.[130] This therapy has also been shown to have a high response rate and a long time to progression (appendix p 4).[131,132] Although early interest in radioembolisation was for locally advanced disease (vascular invasion), two prospective randomised trials[133,134]

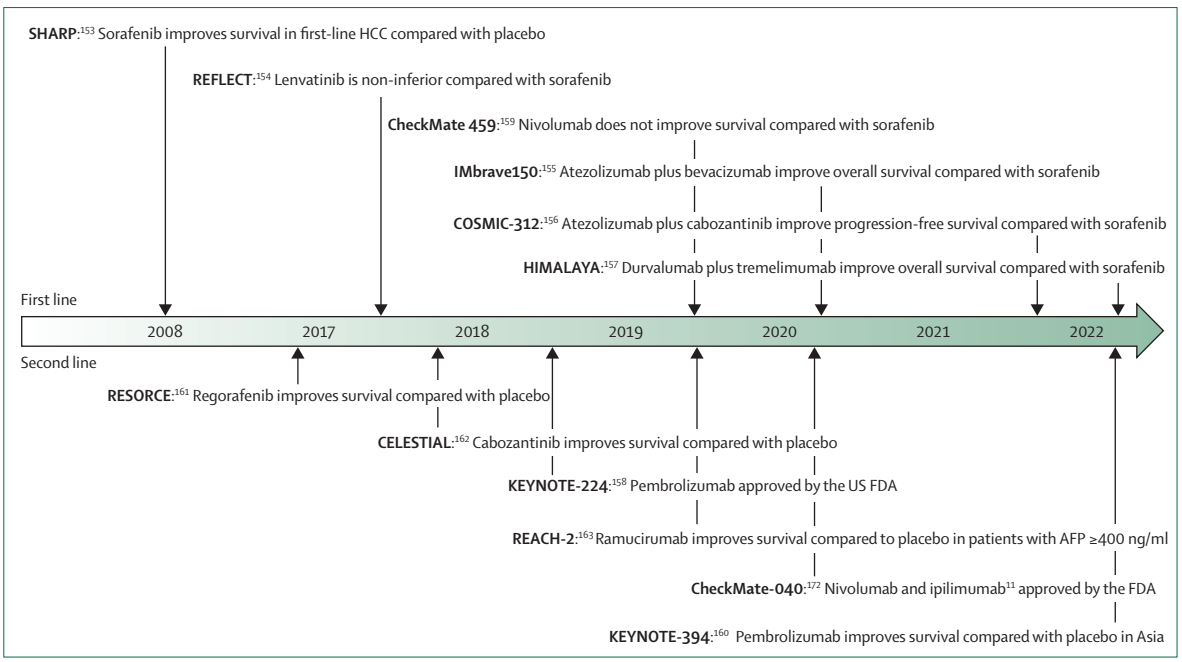

Figure 3: **Milestones in the development of systemic therapy for HCC**
AFP=alpha-fetoprotein. FDA=Food and Drug Administration. HCC=hepatocellular carcinoma.

did not provide evidence to show a survival benefit over sorafenib. In a randomised phase 2 study,[135] the importance of personalised dosimetry was confirmed when significantly higher responses were observed compared with standard dosimetry. In 2021, radioembolisation was included in the curative arm of the BCLC algorithm, with median survival exceeding 50 months.[92]

Several randomised trials have been conducted to evaluate TACE combined with TKIs to improve the efficacy of TACE. Although there were differences in trial design, agent used (sorafenib in SPACE and TACE 2; brivanib in BRISK TA; and orantinib in ORIENTAL), location (SPACE was done in Asia and the USA; BRISK TA was done globally; TACE 2 was done in the UK; and ORIENTAL was done in Japan, South Korea, and Taiwan), and primary endpoint (time to progression in SPACE; overall survival in BRISK TA and ORIENTAL; and progression-free survival in TACE 2), the results of these trials were all negative (appendix p 4).[136–139] With adapted criteria of progression, including time to untreatable progression and progression to TACE refractoriness, the TACTICS trial[140] met one of the coprimary endpoints, in which median progression-free survival significantly increased from 13·5 months with TACE to 25·2 months in patients receiving TACE plus sorafenib (equating to a 41% [p=0·006] reduction in the risk of progression with the addition of the targeted therapy). However, the longer progression-free survival did not translate into a longer overall survival in the experimental arm. Based on promising data from phase 2 studies that evaluated the combination of immune checkpoint inhibitor(ICI)-based therapies with TACE and radioembolisation, this concept is further explored in randomised phase 3 studies.[141–143] Contemporarily, the principles of safely administering intra-arterial therapies are based on angiographic selectivity (preserving hepatic parenchyma) and optimisation of local drug or radiation delivery, as well as a multidisciplinary approach of stage migration to systemic treatments.

Radiotherapy

The main radiotherapy techniques for hepatocellular carcinoma are stereotactic body radiotherapy (SBRT), proton therapy, and interstitial brachytherapy. The local precision of these strategies allows for a high tumour dose and reduces the risk of radiation-induced liver disease. A number of small prospective studies of SBRT in hepatocellular carcinoma reported local control rates of 75–95% 1 year after treatment.[144] These data are supported by large cohort studies and meta-analyses of retrospective studies not only in early hepatocellular carcinoma, but also in patients at high risk with portal vein infiltration.[145–150] SBRT can therefore be considered as a treatment option in palliative settings when other local therapies are not feasible (eg, if there is a high probability of treatment failure, limited liver function, and technical obstacles), but additional prospective trials are required to better define the role of these treatment modalities.[151] In view of the high local tumour control rate, SBRT might also be an interesting alternative to conventional bridging therapies in the context of liver transplantation to reduce the risk of waiting list dropout.[144,152]

Advanced stage

Systemic therapies

Systemic therapy is the preferred treatment modality for patients with advanced stage hepatocellular carcinoma, as well as for patients with intermediate stage hepatocellular carcinoma who do not qualify for local therapies. The survival of patients treated with systemic agents has significantly improved since 2017. With the approval of six treatment regimens by the European Medicines Agency (EMA) and eight regimens by the US Food and Drug Administration (FDA), sequential therapy should be routinely considered for patients with advanced hepatocellular carcinoma (figures 2, 3). Baseline characteristics of the pivotal trials and key efficacy parameters of approved systemic agents are summarised in tables 1 and 2.

First-line therapies

Sorafenib was the first targeted therapy to show efficacy in patients with advanced hepatocellular carcinoma. This TKI targets VEGF receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), rapidly accelerated fibrosarcoma (RAF), and several other tyrosine kinases. In the pivotal SHARP study,[153] median overall survival in the sorafenib arm was 10·7 months versus 7·9 months in patients who were given placebo. Similar results were also shown in a parallel phase 3 study involving patients who were mainly Asian and predominantly affected by HBV.[164] Of note, despite similar data for progression-free survival, overall survival in other phase 3 trials has increased over time in the sorafenib arm, peaking at 15·5 months in the COSMIC-312 study.[156] The reasons for the extended survival are likely to be multifactorial, including differences in inclusion criteria and the use of effective sequential therapies.

Lenvatinib is an oral TKI with activity against VEGFR1–3, FGFR1–4, PDGF, RET, and KIT. In the phase 3 REFLECT study,[154] which mainly enrolled Asian patients, non-inferiority of lenvatinib in comparison to sorafenib was shown in the first-line setting with a median overall survival of 13·6 months in the experimental lenvatinib arm versus 12·3 months in the control (sorafenib) arm. Concerning the key secondary endpoints, median progression-free survival and overall response rate, lenvatinib was superior to sorafenib. Adverse effects were overall slightly more pronounced in patients treated with lenvatinib, particularly hypertension and proteinuria, whereas patients who received sorafenib had more hand foot skin reactions and diarrhoea. Quality of life scores declined with both treatments, but were slightly in favour of lenvatinib.[165] Based on the data from the REFLECT study, lenvatinib has been approved by the EMA and the FDA for the first-line treatment of advanced hepatocellular carcinoma.

IMbrave150 was not only the first phase 3 study to show a significant survival benefit compared with sorafenib, but also the first positive phase 3 study with an ICI-based regimen. The study was interrupted at the first interim analysis having met its primary endpoint by showing improved overall survival with the combination of the VEGF-A antibody bevacizumab with the PD-L1 antibody atezolizumab compared with sorafenib (19·2 months versus 13·4 months in the final analysis).[155,166] Additionally, the confirmed overall response rate and progression-free survival were significantly improved in the atezolizumab plus bevacizumab arm. Despite a similar number of patients with serious adverse events, tolerability and patient reported outcomes were also favourable for the combination arm with a median time to deterioration of quality of life of 11·2 months versus 3·6 months.[167] Because of the increased risk of bleeding associated with the administration of bevacizumab, endoscopies were required within the 6 months before enrolment and screening for varices is strongly advised before treatment initiation in patients with portal hypertension. The IMbrave150 trial marked the transition towards ICI-based therapy for patients with hepatocellular carcinoma and international guidelines endorsed the combination regimen as the new standard of care in front-line treatment of advanced hepatocellular carcinoma.[87–89]

Several promising combinatorial treatment strategies involving ICIs are currently under investigation and data from two additional phase 3 trials[156,157] for first-line treatment of hepatocellular carcinoma have been reported. Based on the unique immunomodulatory and anti-angiogenic profile of the multikinase inhibitor cabozantinib, the COSMIC-312 trial[156] evaluated the efficacy of cabozantinib plus atezolizumab versus sorafenib (with overall survival and progression-free survival as dual primary endpoints) and sorafenib versus cabozantinib single agent (with progression-free survival as a secondary endpoint). The study met one of its dual primary endpoints, and showed a significant improvement in progression-free survival in the combination arm compared with sorafenib in first-line hepatocellular carcinoma (in the final analysis), which, however, did not translate into prolonged median overall survival in the interim analysis. For the secondary endpoint, the evaluation of progression-free survival with the single agents, median progression-free survival was 5·8 months with cabozantinib versus 4·3 months with sorafenib, which also did not reach the threshold of significance at this interim analysis. Grade 3 or 4 toxicities were in line with the side-effect profiles previously reported for cabozantinib, sorafenib, and atezolizumab.

The HIMALAYA trial[157] is the largest phase-3 first-line study conducted in patients with advanced hepatocellular carcinoma, and the first to report outcomes for dual ICI therapy. An initial four-arm design was used to assess the efficacy of combined checkpoint inhibition with durvalumab and tremelimumab (two different treatment regimens) or durvalumab monotherapy compared with sorafenib alone. One of the two dual therapy arms was discontinued and the remaining regimen comprised a

	IMbrave150[155] (n=501)		SHARP[153] (n=602)		REFLECT[154] (n=954)		COSMIC-312[156] (n=649)		HIMALAYA[157] (n=1171)		
	Atezolizumab plus bevacizumab (n=336)	Sorafenib (n=165)	Sorafenib (n=299)	Placebo (n=303)	Lenvatinib (n=478)	Sorafenib (n=476)	Atezolizumab plus cabozantinib (n=432)	Sorafenib (n=217)	Stride (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Baseline characteristics (%)											
ECOG 0	209 (62%)	103 (62%)	161 (54%)	164 (54%)	304 (64%)	301 (63%)	277 (64%)	144 (66%)	244 (62%)	237 (61%)	241 (62%)
ECOG 1	127 (38%)	62 (38%)	114 (38%)	117 (39%)	174 (36%)	175 (37%)	153 (36%)	73 (34%)	148 (38%)	150 (39%)	147 (38%)
BCLC A	8 (2%)	6 (4%)	0	0	0	0	0	0	0	0	0
BCLC B	52 (15%)	26 (16%)	54 (18%)	51 (17%)	104 (22%)	92 (19%)	140 (32%)	72 (33%)	77 (20%)	80 (21%)	66 (17%)
BCLC C	276 (82%)	133 (81%)	244 (82%)	252 (83%)	374 (78%)	384 (81%)	292 (68%)	145 (67%)	316 (80%)	309 (79%)	323 (83%)
EHS	212 (63%)	93 (56%)	159 (53%)	150 (50%)	291 (61%)	295 (62%)	232 (54%)	122 (56%)	209 (53%)	212 (54%)	203 (52%)
MVI	129 (38%)	71 (43%)	108 (36%)	123 (41%)	109 (23%)	90 (19%)	136 (31%)	61 (28%)	103 (26%)	94 (24%)	100 (25%)
VP4	48 (14%)	25 (15%)	NA	NA	Excluded	Excluded	NA	NA	Excluded	Excluded	Excluded
CP A	333 (100%)	165 (100%)	284 (95%)	297 (98%)	475 (99%)	471 (99%)	432 (100%)	217 (100%)	387 (98%)	380 (98%)	379 (97%)
ALBI 1	189 (57%)	81 (52%)	NA	NA	318 (66%)	340 (72%)	NA	NA	217 (55%)	198 (51%)	203 (52%)
ALBI 2	140 (43%)	75 (48%)	NA	NA	158 (34%)	134 (28%)	NA	NA	174 (44%)	189 (49%)	185 (48%)
AFP >400 ng/ml	126 (38%)	62 (37%)	93 (31%)	109 (36%)	163 (46%)*	157 (39%)*	163 (38%)	65 (30%)	145 (37%)	137 (35%)	124 (32%)
Efficacy data											
Median overall survival (months)	19·2	13·4	10·7	7·9	13·6	12·3	15·4	15·5	16·4	16·6	13·8
Progression-free survival (months)	6·9	4·3	5·5	2·8	7·3	3·6	6·8	4·2	3·8	3·7	4·1
Overall survival: HR (95% CI)	0·66 (0·52–0·85)	0·66 (0·52–0·85)	0·69 (0·55–0·87)	0·69 (0·55–0·87)	0·92 (0·79–1·06)	0·92 (0·79–1·06)	0·90 (0·69–1·18)	0·90 (0·69–1·18)	0·78 (0·65–0·93)†	0·78 (0·65–0·93);† 0·86 (0·73–1·03)‡	0·86 (0·73–1·03)‡
Progression-free survival: HR (95% CI)	0·65 (0·53–0·81)	0·65 (0·53–0·81)	0·58 (0·45–0·74)	0·58 (0·45–0·74)	0·66 (0·57–0·77)	0·66 (0·57–0·77)	0·63 (0·44–0·91)	0·63 (0·44–0·91)	0·90 (0·77–1·05)	0·90 (0·77–1·05); 1·02 (0·88–1·19)	1·02 (0·88–1·19)
Overall response rate (RECIST 1.1 criteria)	97 (30%)	18 (11%)	6 (2%	3 (1%)	90 (19%)	31 (7%)	47 (11%)	8 (4%)	79 (20%)	66 (17%)	20 (5%)
Overall response rate (modified RECIST 1.1 criteria)	114 (35%)	22 (14%)	NA	NA	194 (41%)	59 (12%)	NA	NA	NA	NA	NA
Complete responses (RECIST 1.1 criteria)	25 (8%)	2 (<1%)	0	0	2 (<1%)	1 (<1%)	1 (<1%)	0	12 (3%)	6 (2%)	0
Disease control rate (modified RECIST 1.1 criteria)	241 (74%)	87 (55%)	129 (43%)	97 (32%)	348 (73%)	281 (59%)	337 (78%)	140 (65%)	236 (60%)	213 (55%)	236 (61%)
Safety											
≥3 adverse events	Hypertension: 39 (12%); AST increase: 17 (5%); proteinuria: 13 (4%)	Hypertension: 14 (9%); AST increase: 5 (3%); proteinuria: 1 (<1%)	HFSR: 24 (8%); diarrhoea: 24 (8%); fatigue: 12 (4%)	HFSR: 1 (<1%); diarrhoea: 6 (2%); fatigue: 7 (3%)	Hypertension: 111 (23%); bilirubin increase: 31 (7%); proteinuria: 27 (6%)	Hypertension: 68 (14%); bilirubin increase: 23 (5%); proteinuria: 28 (2%)	Hepatic events: 37 (9%); diarrhoea: 18 (4%); rash: 1 (<1%)	Hepatic events: 7 (3%); diarrhoea: 4 (2%); rash: 1 (<1%)	Hepatic events: 23 (6%); diarrhoea: 17 (4%); rash: 6 (2%)	Hepatic events: 17 (5%); diarrhoea: 6 (2%); rash: 1 (<1%)	Hepatic events: 15 (10%); diarrhoea: 16 (4%); rash: 0 (0%)
Subsequent therapies	121 (36%)	86 (52%)	NA	NA	156 (33%)	184 (39%)	87 (20%)	80 (37%)	160 (41%)	168 (43%)	175 (45%)

ALBI=albumin-bilirubin. AFP= alpha fetoprotein. BCLC=Barcelona Clinic of Liver Cancer. CP A=Child-Pugh A. ECOG=Eastern Cooperative Oncology Group. EHS=extrahepatic spread. HFSR=hand foot skin reaction. HR=hazard ratio. MVI=macrovascular infiltration. NA=not applicable. RECIST=Response Evaluation Criteria In Solid Tumors. VP4=vena porta main trunk infiltration. *AFP levels ≥200 ng/ml were reported only in the REFLECT study. In all other studies, the AFP cutoff was 400 ng/ml. †Value refers to comparison of STRIDE *vs* sorafenib. ‡Value refers to comparison of durvalumab *vs* sorafenib.

Table 1: **Baseline characteristics and key efficacy outcome data from positive phase 3 studies (first line)**

	RESORCE[161]		CELESTIAL[162]		REACH-2[163]	
	Regorafenib (n=379)	Placebo (n=194)	Cabozantinib (n=470)	Placebo (n=237)	Ramucirumab (n=197)	Placebo (n=95)
Baseline characteristics (%)						
ECOG 0	247 (65%)	130 (67%)	245 (52%)	131 (55%)	113 (57%)	55 (58%)
ECOG 1	132 (35%)	64 (33%)	224 (48%)	106 (45%)	84 (43%)	40 (42%)
BCLC A	1 (<1%)	0	0	0	0	0
BCLC B	53 (14%)	22 (11%)	42 (9%)	24 (10%)	34 (17%)	20 (21%)
BCLC C	325 (86%)	172 (89%)	427 (91%)	213 (90%)	163 (83%)	75 (97%)
EHS	264 (70%)	147 (76%)	369 (79%)	182 (77%)	141 (72%)	70 (74%)
MVI	110 (29%)	54 (28%)	129 (27%)	81 (34%)	70 (36%)	30 (35%)
VP4	NA	NA	NA	NA	NA	NA
CP A	373 (98%)	188 (97%)	465 (99%)	235 (99%)	197 (100%)	95 (100%)
ALBI 1	164 (43%)	81 (42%)	186 (39%)	102 (43%)	85 (43%)	42 (44%)
ALBI 2	213 (56%)	112 (58%)	282 (61%)	133 (57%)	112 (57%)	53 (56%)
AFP >400 ng/ml	162 (43%)	87 (45%)	192 (41%)	101 (43%)	197 (100%)	95 (100%)
Efficacy data						
Median overall survival (months)	10·6	7·8	10·2	8·0	8·1	5·3
Progression-free survival (months)	3·1	1·5	5·2	1·9	2·8	1·5
Overall survival: HR (95% CI)	0·63 (0·50–0·79)	0·63 (0·50–0·79)	0·76 (0·63–0·92)	0·76 (0·63–0·92)	0·71 (0·53–0·95)	0·71 (0·53–0·95)
Progression-free survival: HR (95% CI)	0·46 (0·37–0·56)	0·46 (0·37–0·56)	0·44 (0·36–0·52)	0·44 (0·36–0·52)	0·45 (0·34–0·60)	0·45 (0·34–0·60)
Overall response rate (RECIST 1.1 criteria)	27 (7%)	6 (3%)	18 (4%)	1 (<1%)	9 (5%)	1 (1%)
Overall response rate (modified RECIST 1.1 criteria)	40 (11%)	8 (4%)	NA	NA	NA	NA
Complete response (modified RECIST 1.1 criteria)	2 (1%)	0%	0%	0%	0%	0%
Disease control rate	247 (65%)	70 (36%)	300 (64%)	79 (33%)	118 (60%)	37 (39%)
Safety						
≥3 adverse events	Hypertension: 57 (16%); HFSR: 47 (13%); bilirubin increase: 39 (11%)	Hypertension: 9 (5%); HFSR: 1 (1%); bilirubin increase: 21 (11%)	HFSR: 79 (17%); hypertension: 74 (16%); diarrhoea: 46 (10%)	HFSR: 0 (0%); hypertension: 4 (2%); diarrhoea: 4 (2%)	Liver failure: 36 (18%); hypertension: 25 (13%); bleeding: 10 (6%)	Liver failure: 15 (16%); hypertension: 5 (5%); bleeding: 3 (3%)
Subsequent therapies	76 (20%)	54 (28%)	118 (25%)	71 (30%)	53 (27%)	27 (27%)

AFP=alpha fetoprotein. ALBI=albumin-bilirubin. BCLC=Barcelona clinic liver cancer. CP A=Child-Pugh A. ECOG=Eastern Cooperative Oncology Group. EHS=extrahepatic spread. HFSR=hand foot skin reaction. HR=hazard ratio. MVI=macrovascular infiltration. NA=not applicable. RECIST=Response Evaluation Criteria In Solid Tumors. VP4=vena porta main trunk infiltration.

Table 2: **Baseline characteristics and key efficacy outcome data from positive phase 3 studies (second line)**

single priming dose of tremelimumab and durvalumab every 4 weeks (the single tremelimumab regular interval durvalumab [STRIDE] regimen). The trial showed that there was a significant improvement in overall survival for the combination arm compared with sorafenib, thus meeting its primary endpoint. In addition, non-inferiority of durvalumab compared with sorafenib as front-line therapy in patients with advanced hepatocellular carcinoma was reported. Although overall response rate was higher with durvalumab and tremelimumab and durvalumab compared with sorafenib, data for progression-free survival were nearly identical, suggesting that progression-free survival is not a reliable surrogate for overall survival for patients with hepatocellular carcinoma treated with ICIs, as in other cancers.

The single dose of tremelimumab doubled the rate of grade 3 and 4 treatment-related adverse events, as well as the number of patients who required treatment with high dose steroids (20·0%) in comparison to durvalumab monotherapy (9·5%). Currently, neither the STRIDE regimen or durvalumab monotherapy is approved, and atezolizumab plus bevacizumab remains the only ICI-based therapy for hepatocellular carcinoma approved by both the EMA and FDA. In addition, the FDA granted accelerated approval for nivolumab (in March, 2020) and ipilimumab and pembrolizumab (in November, 2018) for second-line therapy based on phase 1 and 2 efficacy data from KEYNOTE-224 and CheckMate 040.[158, 168] Subsequent phase 3 trials of first-line nivolumab and second-line pembrolizumab did not meet their primary endpoints,

although the KEYNOTE-394 trial reported positive results for pembrolizumab in an Asian population.[159,160,169]

Second-line therapies

Regorafenib is an oral fluorinated sorafenib analog with a similar spectrum of molecular targets. The randomised controlled RESORCE phase 3 trial[161] evaluated the role of regorafenib in patients after progression on sorafenib and was the first positive trial in the second-line setting for patients with advanced hepatocellular carcinoma. In contrast to other phase 3 trials in second-line, tolerability of sorafenib was required for enrolment. The trial reached its primary endpoint by showing a significant improvement in median overall survival for regorafenib over placebo. The spectrum of adverse events was similar to the side-effect profile for sorafenib. Based on the results of the study, regorafenib was approved in 2017 by the FDA and EMA for the treatment of patients with advanced hepatocellular carcinoma who tolerated, but progressed, on sorafenib.

Cabozantinib, a tyrosine kinase inhibitor with activity against multiple targets including MET, VEGFR, and the TAM kinase family (TYRO-3, AXL, and MER), is endorsed by both the EMA and the FDA as a second-line treatment for patients with advanced hepatocellular carcinoma. The approval of cabozantinib was based on the improved overall survival (10·2 months for cabozantinib *vs* 8·0 months for placebo), that was shown in the phase 3 CELESTIAL trial,[162] which compared cabozantinib to placebo in second-line and third-line patients with preserved liver function and good performance status. Despite a low overall response rate, median progression-free survival was extended and a quality of life analysis favoured cabozantinib over placebo.[170] In contrast to the other second-line trials, the CELESTIAL study included patients who had more than one previous therapy, and provided preliminary evidence in the third-line setting.

Ramucirumab, a recombinant monoclonal antibody that binds to and inhibits VEGFR-2, was the first intravenous, non-TKI to become available for the treatment of advanced hepatocellular carcinoma. Although the initial phase 3 REACH study[171] did not provide evidence that ramucirumab improves median overall survival for patients who received previous therapy with sorafenib, a subgroup analysis showed an overall survival benefit, specifically in patients with a baseline AFP level ≥400 ng/ml; a finding that could be confirmed in the subsequent REACH-2 study.[163] An additional pooled meta-analysis of prospectively collected quality of life data showed that there was a statistically significant benefit of ramucirumab over placebo, and was notable for being the first comprehensive analysis of phase 3 data that shifted quality of life into the focus of clinical decision making in advanced hepatocellular carcinoma.[173] Overall, although ramucirumab is an option for patients with hepatocellular carcinoma with an AFP ≥400 ng/ml, it is not necessarily the agent of choice for this population, considering the treatment benefit of TKIs independent of AFP.

Assessment of response

Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 is the gold standard for radiologic response assessment.[174] In brief, RECIST 1.1. measures the sums of the maximum diameters of target lesions at baseline, and subsequently measures the change during follow-up. Although RECIST 1.1 criteria were developed to capture response assessment under systemic therapies that impart cytostatic or cytotoxic effects, modified RECIST (mRECIST) criteria were developed specifically for hepatocellular carcinoma in the setting of molecular-targeted therapies or locoregional therapies.[175,176] The development of the mRECIST criteria stemmed from two key assumptions related to hepatocellular carcinoma: first, hepatocellular carcinoma is a hypervascular tumour, and response might not only be manifested by lesional size reduction, but also by loss of vascularity (representing necrosis). Furthermore, it was previously thought that hepatocellular carcinoma tumours occurring in a background of liver cirrhosis would be less likely to undergo anatomical reduction despite effective treatment. As a result, mRECIST criteria have become an ancillary method of reporting response in addition to RECIST 1.1, particularly when attempting to adequately capture the necrosis-inducing treatment effect from local and systemic therapies.[177,178] The extent of reduction of enhancement translates to the response declared in a manner analogous to RECIST 1.1 (eg, a 20% decrease in enhancement is considered a partial response). In the era of immunotherapy, which induces radiological shrinkage, RECIST 1.1 has been the standard method of response assessment in clinical trials. Immune RECIST, that mandates confirmation of PD, has not been widely adopted in hepatocellular carcinoma and would benefit from inclusion as an exploratory endpoint to provide validation of its use.

Of note, response to preoperative therapies could be used as a dynamic biomarker of improved outcomes following surgery and transplantation. In addition, response to therapies also correlates with longer survival after locoregional and systemic therapies in more advanced disease.[177–179]

Transition between local and systemic therapies for intermediate stage hepatocellular carcinoma

To ensure that patients are matched with the optimal therapy, clinical decision making requires a multidisciplinary team that longitudinally re-evaluates and adapts therapeutic strategies. Although local therapies remain the mainstay of early disease stages, there is currently a paradigm shift in patients with intermediate hepatocellular carcinoma. As a result of the substantial progress in systemic treatments, a critical review of the indication for locoregional therapies is mandatory. Studies have provided evidence that median overall survival with

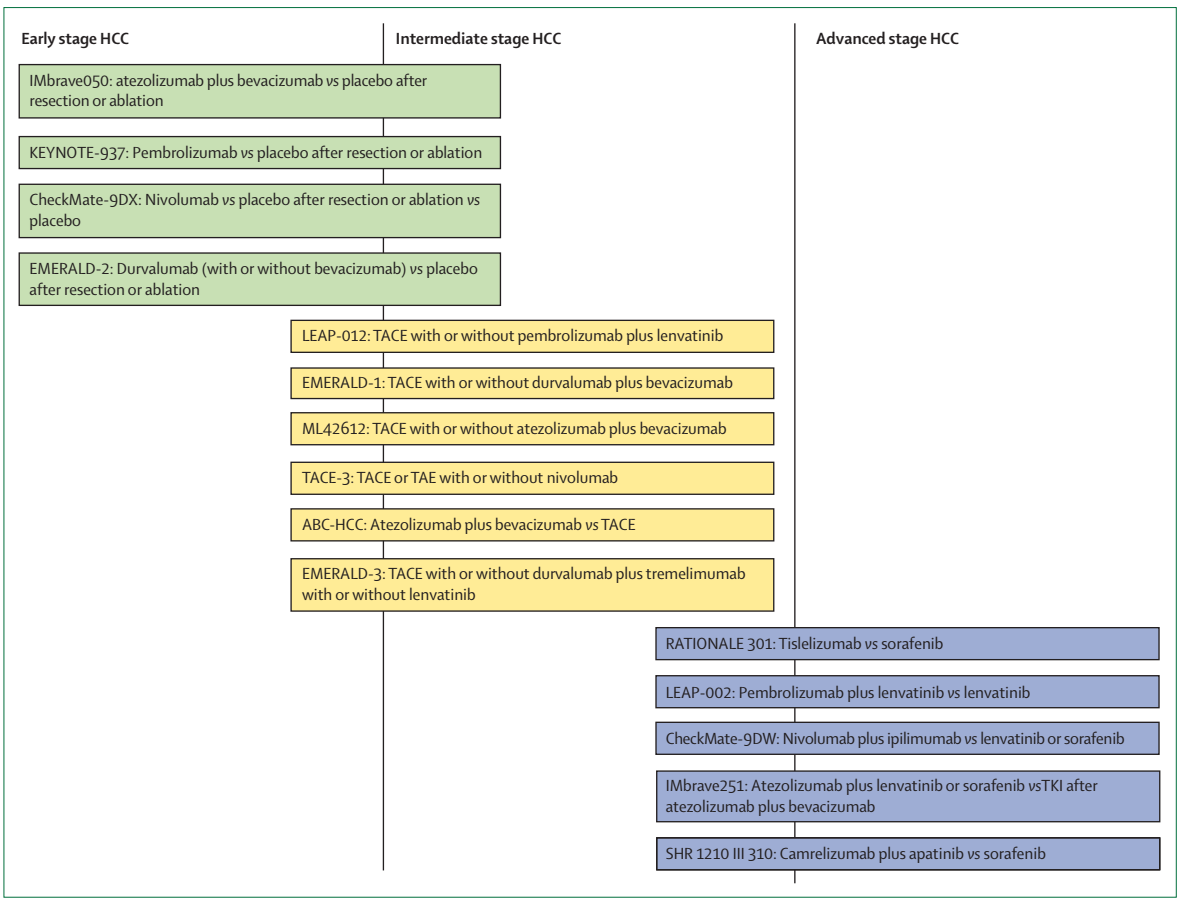

Figure 4: **Ongoing immunotherapy-based phase 3 trials in HCC**
HCC=hepatocellular carcinoma. TAE=bland particle embolisation. TACE=transarterial chemoembolisation. TKI=tyrosine kinase inhibitor.

TACE is significantly worse in unselected patient populations (median overall survival <20 months) compared with selected patients with maintained liver function and small tumours (30–45 months).[180,181] Guidelines therefore recommend TACE in patients with liver-limited disease, a tumour size <7 cm, no macrovascular infiltration, a preserved liver function, and a good Eastern Cooperative Oncology Group (ECOG) performance status. Prognostic scores, such as the hepatoma arterial-embolisation prognostic score, could also help to select patients that are most likely to benefit from treatment.[181–183]

Apart from the identification of optimal candidates for local therapies, the appropriate time to transition from local to systemic therapies must not be missed. Although repeated use of locoregional therapies is possible, by doing so, patients are at risk of cumulative liver injury and acute and chronic deterioration of liver function, thereby jeopardising options for subsequent systemic treatment.[184–186] Increasing evidence suggests that patients who only reach disease stabilisation after TACE, but do not reach a deep response, are likely to have a poor prognosis and are not likely to benefit from additional local therapies.[181]

Earlier conversion towards systemic therapies, rather than repetitive use of embolisation, is advocated in the event of the development of extrahepatic spread, or progressive venous involvement, particularly in patients without a radiological response.[187] A longitudinal response assessment and close monitoring of liver function is mandatory to allocate patients to either local or systemic therapies.

Sequencing and decision making for systemic therapy

The selection of systemic therapy for an individual patient is influenced by several factors, including efficacy, and toxicity, as well as the presence of contraindications or predictive factors. Special populations (eg, people living with HIV, patients on haemodialysis, or patients with cardiovascular events) are usually excluded from clinical trials, and the standard of care for these patients is poorly defined. In general, patients should have Child-Pugh A liver disease and an ECOG performance status of 0 to 1, consistent with the population in which the evidence base was generated. Although treatment might be tolerated outside of these criteria, there is no evidence of benefit and

outcomes are generally poor.[188–190] For most patients, combination therapy, including a PD1 or PD-L1 inhibitor, represents the first-line treatment of choice. Hence, the combinations of both atezolizumab plus bevacizumab, and durvalumab plus tremelimumab, if approved by the FDA and the EMA, could be considered.[155,157] Atezolizumab plus cabozantinib did not show an overall survival benefit compared with sorafenib, which makes this combination a less attractive option compared with other ICI-based regimens.[156] Although atezolizumab plus bevacizumab was associated with a higher response rate and more impressive hazard ratio than durvalumab plus tremelimumab, cross-trial comparisons are unreliable because of distinct patient populations included in these trials, and both regimens should be considered as effective first-line options. Additional considerations include the side-effect profile; for example, bevacizumab is associated with an increased risk of variceal haemorrhage and upper endoscopy is recommended to ensure varices are adequately treated.[191] Despite esophagogastroduodenoscopy (EGD) and treatment of varices being mandated in the IMbrave 150 trial,[155] 8 (2·4%) patients had a variceal haemorrhage and four patients died of gastrointestinal bleeding. The HIMALAYA trial[157] did not mandate EGD and no variceal bleeding was reported. However, it should be noted that patients with advanced portal vein thrombosis classified as Vp4 were excluded from the HIMALAYA trial but not from the IMbrave150 trial. Thus, for patients deemed to be at risk of bleeding, the dual checkpoint regimen might be preferred. Regarding quality of life assessment, a significant delay in deterioration of patient reported outcomes has been reported for atezolizumab plus bevacizumab as well as for durvalumab plus tremelimumab and for durvalumab compared with sorafenib.[157,167] As of July, 2022, no validated predictive markers have been identified for ICI therapy in hepatocellular carcinoma. On the basis of pre-clinical data and a meta-analysis of three clinical trials, a potential negative predictive value of NASH and non-viral liver disease for ICI efficacy in patients with hepatocellular carcinoma was suggested,[192] but could not be confirmed in subgroup analyses from the HIMALAYA trial or other trials in the preoperative setting.[61,111] Therefore, at this point, there are no conclusive data that advocate for clinical decision making based on underlying liver disease.

Despite the success of recent trials, some patients have contraindications to ICI therapy, including patients who have severe autoimmune disorders and patients living with an essential organ transplant. For these patients, treatment with single agent sorafenib or lenvatinib are appropriate first-line agents. Given their equivalent efficacy in terms of survival, additional factors, such as the higher response rate and superior progression-free survival for lenvatinib compared with sorafenib, can be considered when choosing a first-line strategy.[154]

In the second-line setting, the only evidence-based sequences are for regorafenib, cabozantinib, or ramucirumab following first-line sorafenib. There are no meaningful differences in efficacy for any of these drugs evaluated in the second-line setting and the best treatment sequences of the available drugs have not been established. As of July, 2022, second-line therapy after lenvatinib or ICI-based combinations has not been systematically evaluated, but trials are ongoing to help to address this evidence gap (figure 4). In the meantime, international guidelines recommend the use of approved drugs following ICI-based combinations and lenvatinib, and prospective data collection or registries could provide further data in due course.[87]

Current developments

ICI-based therapies are now an integral part of systemic treatment for advanced hepatocellular carcinoma and are currently being explored in all disease stages, from neoadjuvant therapy[109,110] and adjuvant therapy in early hepatocellular carcinoma, over head-to-head comparisons and combinations with local therapies in intermediate stage disease, to treatment-beyond-progression concepts in advanced disease (figure 4). In addition to ICI-based therapies, current strategies are exploring biomarker-driven approaches (eg, that target the FGF19-FGFR4 pathway)[193] or combination therapies that inhibit compensatory signalling pathways that are suspected to cause therapy resistance (eg, feedback activation of the EGFR-PAK2-ERK5 pathway as a mediator of resistance to lenvatinib).[194] Synthetic lethality concepts (eg, combining LXRα activation and RAF inhibition)[195] or strategies to induce vulnerabilities (eg, combining CDC7 and mTOR inhibitors)[196] could further diversify hepatocellular carcinoma therapies. To realise precision medicine in hepatocellular carcinoma in the future, biomarkers need to be established that guide treatment decisions in all stages of hepatocellular carcinoma.

Future perspectives

The epidemiology of liver cancer is changing and will increasingly be dominated by non-viral causes. Innovative surveillance and preventive strategies will be needed to address the rising incidence of hepatocellular carcinoma in patients with fatty liver disease. Despite substantial progress made in locoregional and systemic therapy, most patients are likely to not respond and ultimately succumb to their disease. Consequently, more effective systemic therapies are still required, along with predictive biomarkers that enable personalised and cost-effective treatment stratification. The dynamic interplay between locoregional and systemic therapy is also being explored. Having been one of the most challenging cancers with the poorest outlook, there are reasons to be optimistic that the coming years will continue to lead to improved outcomes.

Contributors
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