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Hepatocellular carcinoma: Epidemiology, diagnosis and treatment☆

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Summary

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide and primarily affects individuals with cirrhosis. While viral hepatitis has historically been the predominant cause, the burden of HCC is increasingly shifting toward non-viral aetiologies, such as ALD (alcohol-related liver disease) and MASLD (metabolic dysfunction-associated steatotic liver disease). Preventive strategies, including HBV vaccination and antiviral therapies, have reduced the incidence of virus-related HCC, while emerging antifibrotic and metabolic agents may limit MASLD progression. Surveillance with biannual ultrasound and alpha-fetoprotein testing facilitates early detection and curative treatment, although underuse remains a critical limitation. Advances in surgical resection, liver transplantation, and locoregional therapies have improved outcomes in early and intermediate stages. In advanced HCC, immune checkpoint inhibitor-based combinations have shifted the treatment landscape, with median overall survival now exceeding two years and long-term responses observed in a subset of patients. Despite these advances, substantial unmet needs remain in prevention, early detection, and therapeutic access. Ongoing research into biomarkers and novel treatments offers the potential to further transform the HCC care continuum.

Introduction

Hepatocellular carcinoma (HCC) accounts for ∼85-90% of all liver cancers. HCC is currently the leading cause of cancer-related death among patients with cirrhosis and is a major public health problem.[1,2] HCC has a cure rate of around 25% and an overall 5-year survival rate below 30%.[1,2] Vaccination for HBV infection and antiviral therapies for both HBV and HCV have reduced the incidence of HCC associated with these aetiologies,[1] but the global rise in metabolic dysfunction-associated steatotic liver disease (MASLD)-related HCC presents new challenges.[2–4]

Advances in surgical techniques and locoregional therapies have led to improvements in outcomes for early and intermediate tumours, with projected median overall survival (mOS) of >60 months and ∼30 months, respectively.[1,5] However, ∼50-60% of patients will be diagnosed at, or progress to, an advanced stage of the disease, where the reported natural history is short (mOS: 6-8 months).[1,5] Immunotherapies have substantially transformed outcomes in advanced HCC, with current first-line combination regimens achieving a mOS of 16–24 months and durable long-term responses, resulting in approximately 25% of patients surviving at 3–4 years.[6–8] This review summarises the current understanding of epidemiology, prevention, surveillance, diagnosis, and treatment strategies, with a final word on novel therapies.

Methods

A PubMed search was conducted to identify English language articles describing observational studies, randomised clinical trials, meta-analyses and systematic reviews on HCC published between January 1st 2010, and February 20th 2025 (supplementary information).

Epidemiology and risk factors

Primary liver cancer is the sixth most common cancer globally and the third leading cause of cancer-related death worldwide.[9] HCC comprises ∼85–90% of primary liver cancer cases and typically arises in the context of cirrhosis due to chronic liver disease associated with HBV and HCV infections, alcohol-related liver disease (ALD), and MASLD.[1,2,10] HCC risk is elevated in older individuals, with higher age-standardised incidence rates (ASR) in men than women (ratio 1.2-3.6).[1,2]

The global burden of liver cancer reflects geographic differences in the distribution of risk factors. Approximately 70% of global liver cancer cases occur in Eastern Asia, South-Eastern Asia, and Africa, with an average ASR ranging from 8.5 to 14.7 cases per 100,000 individuals, with the highest incidence rates of 96.1 in Mongolia. In contrast, liver cancer incidence is lower in the Americas and Europe (ASR 5.1 to 5.7

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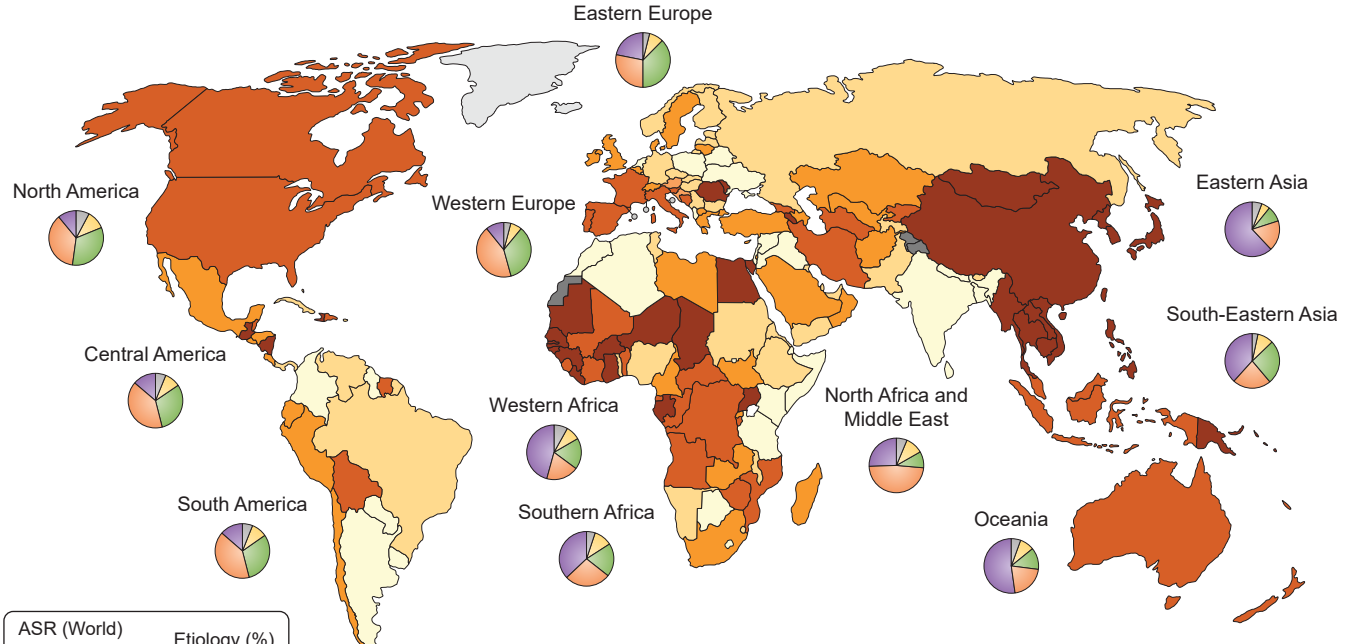
Keypoints

- HCC is a major global health concern, with an estimated 1 million new cases projected in 2025, increasingly linked to ALD and MASLD.
- HBV vaccination and antiviral therapy have reduced viral related HCC, while antifibrotic and metabolic agents may prevent the progression of MASLD towards cancer.
- Surveillance with ultrasound and AFP enables early detection but remains underused, with <50% adherence in Western populations.
- Curative therapies (resection, ablation, transplantation) are applicable in ~25% of patients, with >60-month median survival in early stages.
- In intermediate-stage HCC, combining locoregional treatments with immunotherapy improves progression-free survival and may extend overall survival.
- Immunotherapy-based regimens in advanced HCC are associated with median survival of ~2 years and durable responses, with up to 25% of patients achieving 4-year survival.
- Major gaps include limited access to prevention, suboptimal surveillance uptake, and slow integration of biomarkers and novel therapies.

per 100,000 individuals, respectively) (Fig. 1).[9] Chronic HBV infection remains the leading cause of liver cancer-related deaths worldwide, accounting for ~40% of cases, followed by HCV infection (29.3%), ALD (18.7%), and MASLD (7.2%).[11] However, these proportions vary significantly by region. In Eastern Asia, endemic HBV infection accounts for up to 62% of liver cancer-related deaths, whereas in North America, HCV and ALD play a larger role, contributing 36.8% and 33.5% of cases, respectively.[11] HCV is the leading cause in Western Europe (37%), whereas ALD predominates in Central and Eastern Europe (50%).[2] In recent decades, targeted public health policies, including neonatal HBV vaccination, expanded access to effective antiviral treatments, and widened screening programmes, have led to an epidemiological shift, with non-viral aetiologies increasingly contributing to HCC.[2,12]



Regions	ASR (range)	Number of new cases in 2022***	Prediction for 2045 (%)
North America	6.7 (5.9-6.8)	48,485	+31.1
Europe	5.1 (2.6-10.1)	88,871	+27.4
Asia*	10.0 (1.2-96.1)	607,361	+68.7
Rest of the world**	7.2 (1.1-32.0)	121,419	+98.8

Fig. 1. Global trends and risk factors for HCC. Global distribution of HCC, distribution of most common aetiologies of chronic liver disease and prediction of new HCC cases by 2045 per region. *China: number of new cases in 2022: 367.657; **Number of new cases in 2022 in Africa (73.844), Latin America and the Caribbean (42.769) and Oceania (4.806); ***Prediction of new cases of primary liver cancer estimated to be 1 million by 2025. ASR, age standardised incidence rate; HCC, hepatocellular carcinoma; MASLD, metabolic-associated steatotic liver disease. Adapted from "Hepatocellular carcinoma." (Llovet *et al.* Nat Rev Dis Primers. 2021;7 (1)) and Global Cancer Observatory, World Health Organization (Copyright 2024).

MASLD is the fastest growing aetiology of liver disease worldwide and ranks as the most common liver disease globally, with a prevalence ranging from 25.1% in Western Europe to ~40% in the Americas region.[13] The increasing burden of MASLD-related HCC is closely linked to rising obesity and metabolic risk factors, with projections indicating a 146% increase in cases by 2030.[13] The prevalence of metabolic dysfunction-associated steatohepatitis (MASH), its most severe form, occurs in ~25% of patients in MASLD.[13,14] A meta-analysis of 168,571 individuals with MASH found that ~38% of HCC cases occurred in patients without cirrhosis. Nonetheless, the estimated annual incidence of HCC in non-cirrhotic MASLD remains much lower at 0.02%, compared to 0.5%-2.6% in individuals with cirrhosis.[15]

Several co-factors have been described, which do not induce HCC *per se* but effectively enhance the risk of cancer once a baseline risk factor (viral or non-viral) is present.[16] For instance, aflatoxins contaminate various foods and produce a point mutation in *TP53*, enhancing HBV-related HCC.[17] Similarly, germline *PNPLA3* mutations are associated with a higher risk of HCC development in patients with ALD or MASLD.[18] In addition to *PNPLA3*, *TM6SF2* variants promote hepatic lipid retention and increase HCC risk, whereas *HSD17B13* loss-of-function alleles are protective, mitigating inflammation and reducing HCC susceptibility in ALD and MASLD.[18–21]

Overall, the global incidence of HCC has plateaued, although the absolute number of cases continues to rise due to population growth. The current global distribution of HCC per country and regional differences in aetiology are shown in Fig. 1, which also includes the projected incidence for 2045.

Prevention

The rising incidence of HCC and its shifting risk factors underscore the need for robust preventive measures aimed at slowing or blocking the progression of chronic liver disease. These measures are classified into three categories: primary prevention (preventing the onset of risk factors), secondary prevention (eradication of HCC-related risk factors or increasing early-stage HCC detection), and tertiary prevention (preventing HCC recurrence after curative therapies) (Table 1).

Regarding HCC prevention, a sustained decline in incidence has been well documented following the implementation of universal HBV vaccination for newborns.[22,23] Consequently, this approach has been adopted in clinical guidelines, which advocate for universal HBV vaccination.[19,20] Antiviral therapies are recommended by guidelines to prevent HCC development in patients with chronic HBV or HCV infections.[24–26] In individuals with chronic HBV, treatment with nucleos(t)ide analogues, such as tenofovir and entecavir, reduce the risk of HCC [27] demonstrating a more potent effect than other nucleos(t)ide analogues.[28] Likewise, in chronic HCV infection, direct-acting antivirals lower the risk of HCC.[29] HDV co-occurs with HBV in 4.5% of HBsAg-positive patients and increases the risk of HCC development by 2-3 fold.[30] The impact of HBV/HDV inhibitors, such as bulevirtide, on HCC development has not yet been established.[31]

Overall, cessation of alcohol or tobacco use, physical activity and weight loss are currently recommended for HCC prevention in clinical guidelines.[19,20] In addition, coffee intake has been linked to an inverse, dose-dependent relationship with HCC risk, and is also recommended.[19,20] Conversely, statins, metformin and aspirin, despite being associated with

Table 1. Prevention strategies for hepatocellular carcinoma development.

	Primary prevention: To avoid at-risk status	Secondary prevention: To reduce HCC incidence, and mortality through early detection	Tertiary prevention: To reduce HCC recurrence
AASLD[19] (Level of evidence and grade of recommendation)	• HBV vaccination ***(2, strong)*** • Lifestyle changes, abstinence of alcohol and tobacco, control of metabolic risk factors ***(3, strong)*** • Coffee ***(5, weak)***	• Screening in at-risk populations with ultrasound and AFP every 6 months ***(2, strong)*** • Contrast-enhanced MRI, in select patients in whom US-based surveillance is suboptimal ***(3, weak)*** • Antiviral therapy for HBV and/or HCV ***(2, strong)***	• Antiviral treatment after curative therapy for HCC ***(2, strong)***
EASL[20] (Level of evidence and grade of recommendation)	• HBV vaccination ***(3, strong)*** • Lifestyle changes, abstinence of alcohol and tobacco, control of metabolic risk factors ***(2, weak)*** • Coffee ***(3, weak)***	• Screening in at-risk populations with US and AFP every 6 months ***(3, strong)*** • Anti-viral therapy for HBV and/or HCV ***(2, strong)***	• Antiviral treatment after curative therapy for HCC ***(3, weak)***
ESMO[21] (Level of evidence and grade of recommendation)	• HBV vaccination ***(2, strong)***	• Screening in at-risk populations with US and AFP every 6 months ***(2, strong)*** • Antiviral therapy for HBV and/or HCV ***(3, strong)***	• Antiviral treatment after curative therapy for HCC ***(4, moderate)***
Emerging strategies with limited evidence	• Lifestyle interventions • GLP-1 RAs • Bariatric surgery	• HCC risk stratification • GALAD • Liquid biopsy panel • Aspirin • Metformin • GLP1 RAs • SGLT-2i • Statins • Bariatric surgery • Resmetirom	• Neo- and adjuvant therapies

AFP, alpha-fetoprotein; GALAD, gender, age, AFP-L3%, AFP, and DCP model; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HCC, hepatocellular carcinoma; SGLT2i, sodium-glucose cotransporter 2 inhibitors; US, ultrasound.

reduced HCC risk in observational studies, are not yet recommended, pending prospective investigations (NCT03024684, NCT03654053).[19,20,32]

The advent of new drugs that promote MASH resolution and mitigate fibrosis may curb the progression of chronic liver disease, and thus HCC development. Semaglutide, a GLP-1R agonist, and resmetirom, a thyroid hormone beta-receptor agonist, have demonstrated significant efficacy in resolving MASH and improving liver fibrosis in phase III trials.[33,34] Nonetheless, only retrospective data indicate that they might lower HCC risk, and thus more robust data is awaited.[35]

Surveillance and diagnosis

The aim of surveillance is to reduce cancer-related mortality. This effect has only been observed in one RCT describing a 37% decrease in HCC-related death,[36] although several cohort studies support the use of surveillance for detection of early tumours when they are amenable to curative therapies.[2,37] Consequently, scientific societies endorse surveillance to improve early HCC detection in at-risk patients (Fig. 2).[19–21] Populations at risk of HCC are defined as those with an annual incidence of ≥1% (cirrhosis) or ≥0.2% (chronic hepatitis).[2] In other circumstances, such as non-cirrhotic MASLD or HCV, surveillance is not cost-effective, and thus not recommended.[2,38]

Clinical practice guidelines recommend semi-annual HCC surveillance based on tumour doubling times, using abdominal ultrasound and alpha-fetoprotein (AFP).[19–21] Semi-annual intervals have been shown to be non-inferior to quarterly intervals[39] but superior to annual surveillance.[40] Abdominal ultrasound and AFP are complementary, yielding a sensitivity of ~63% and specificity of 84% for early-stage HCC detection (Fig. 2).[41] Ultrasound performance is operator-dependent and its accuracy is decreased in obese patients, where MRI- or CT-based surveillance could be considered.[19,21] Surveillance effectiveness is also plagued by underuse due to a combination of patient and provider barriers to implementation,[42] and its current use is suboptimal in Western countries (~43% in Europe and ~18% in the USA) and in Asia.[43] Appropriate recall policies have been demonstrated to increase usage of surveillance.[44]

The recommended HCC surveillance tools (ultrasound and AFP levels) have been in use for more than 20 years. None of the novel imaging-based strategies or blood-based biomarkers have been tested at advanced stages – phase IV/V – of the surveillance test approval pathways.[45–47] Abbreviated MRI is the most promising imaging-based strategy, with preliminary data showing a sensitivity of 85%, outperforming ultrasound in two Korean studies.[48,49] Phase IV studies comparing this modality with current standard surveillance are ongoing. Among blood-based markers, three strategies are emerging: a) GALAD score, a panel combining AFP, AFP-L3, and des-carboxy prothrombin with patient age and sex, b) DNA methylation markers and c) circulating tumour DNA markers used in multicancer detection platforms.[50–52] These strategies showed promising results in phase II-III and are currently moving to more advanced stages of development (Fig. 2).[2,19]

Patients with cirrhosis and abnormal surveillance results (*i.e.* liver lesions ≥1 cm or AFP levels ≥20 ng/ml or increasing) should undergo diagnostic testing with dynamic contrast-enhanced MRI or multi-phase CT.[19–21] Liver lesions in at-risk patients undergoing HCC surveillance are graded using a standardised nomenclature (LI-RADS) on a scale from LI-RADS 1 ("definitely benign") to LI-RADS 5 ("definitely HCC") based on imaging features such as maximum diameter, arterial phase hyperenhancement, delayed portal phase washout, and capsule appearance (Fig. 3).[19,53] Diagnostic accuracy for HCC is proportional to LI-RADS category, increasing from 0% for LI-RADS 1 lesions to 94% for LI-RADS 5 lesions.[54] According to current guidelines, a LI-RADS 5 classification establishes an imaging-based HCC diagnosis, while biopsy is advised for

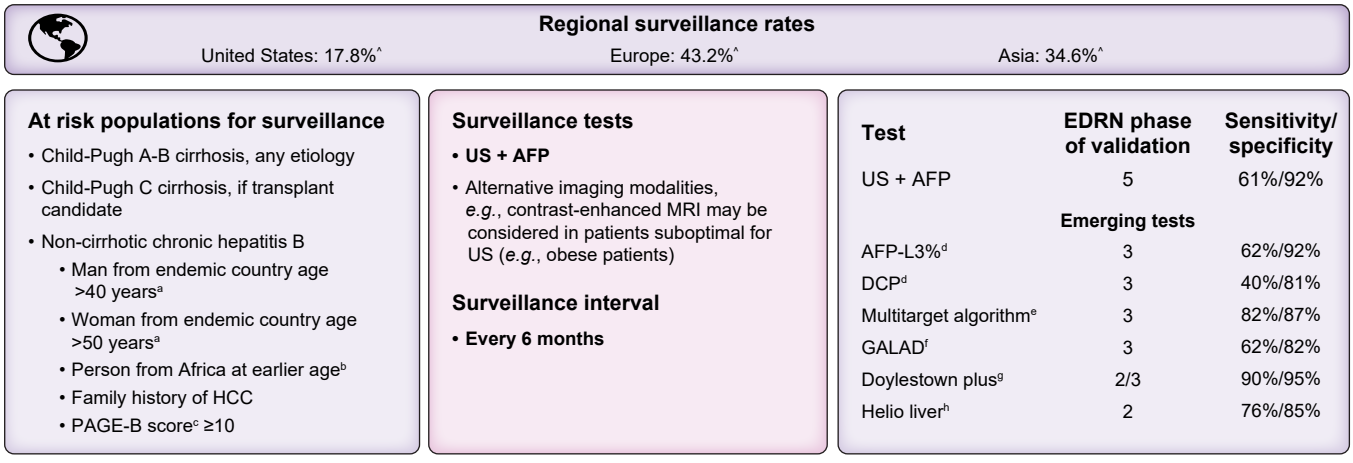
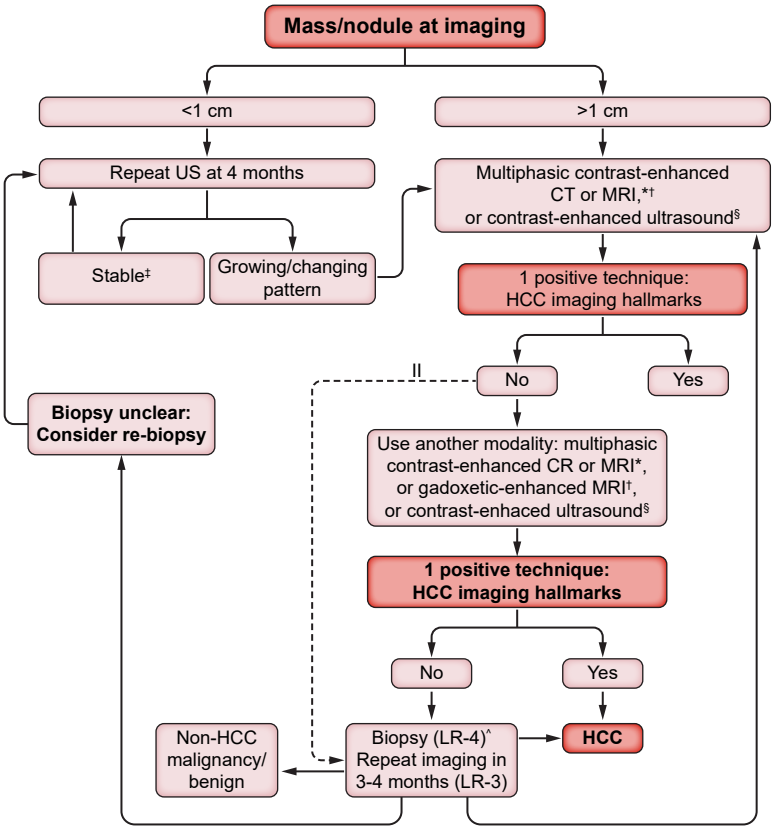


Fig. 2. At risk populations for surveillance, surveillance tests, and regional surveillance rates. [a]An endemic country, as outlined by the AASLD hepatitis B virus guidelines; [b]Surveillance may begin as early as the third decade of life, considering the median age of 46 yrs at HCC diagnosis; [c]Alternative risk calculators may also be used, although PAGE-B has been validated in Western populations undergoing antiviral therapy; [d]Choi J *et al.* Hepatology 2019; 69(5):1983-1994; [e]Chalasani NP *et al.* Clin Gastroenterol Hepatol. 2022; 20(1):173-182; [f]Marsh *et al.* Gastroenterology 2024; 168(2):316-326; [g]Wang M *et al.* Cancer Epidemiol Biomarkers Prev 2017; 26(5):795-803; [h]Lin *et al.* Hepatol Commun. 2022;6(7):1753-1763; .Wolf *et al.* Hepatology 2021; 73(2):713-725. AFP, alpha fetoprotein; AFP-L3%, Lens culinaris lectin binding subfraction of AFP; DCP, des-gamma carboxyprothrombin; GALAD, gender, age, AFP-L3%, AFP, and DCP model; HCC, hepatocellular carcinoma; US, ultrasound; EDRN, Early Detection Research Network; EMR, electronic medical record; RCT, randomised controlled trial.



CT/MRI diagnostic table

Arterial phase hyper-enhancement (APHE)		No APHE		Nonrim APHE		
Observation size (mm)		<20	≥20	<10	10-19	≥20
Count additional major features: • Enhancing "capsule" • Non-peripheral "washout" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4/LR-5	LR-5
	≥Two	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4/LR-5 Observations in this cell are categorized based on one additional major feature:
- LR-4 – if enhancing "capsule"
- LR-5 – if non-peripheral "washout" *OR* threshold growth

Fig. 3. Diagnostic algorithm in cirrhosis and LI-RADS diagnostic table. (A) Algorithm for diagnosis in cirrhosis and (B) LI-RADs system using CT and MRI. *Using extracellular MRI contrast agents or gadobenate dimeglumine; †Diagnostic criteria on gadoxetic acid-enhanced MRI: APHE and washout on the portal venous phase; ‡Lesion <1 cm stable for 12 months (three controls after 4 months) can be shifted back to regular 6-month surveillance; §Diagnostic criteria: APHE and mild washout after 60 s; ‖Optional for center-based programmes. Biopsy is recommended in patients with LI-RADS-M lesions, lesions in non-cirrhotic liver disease, and some LR-3/4 lesions depending on clinical context. APHE, arterial phase hyperenhancement, HCC, hepatocellular carcinoma; (1A) modified from EASL Clinical Practice Guidelines for HCC. J Hepatol 2018; doi: 10.1016/j.jhep.2018.03.019, and (1B) reprinted with permission from the American College of Radiology Committee on LI-RADS.

lesions arising in non-cirrhotic livers, LI-RADS-M (malignant non-HCC lesions) and certain LR-3/4 lesions, depending on clinical context and whether the result will influence patient management.[19–21] ESMO recommends biopsy confirmation prior to initiating systemic therapy in advanced HCC (Level III, Grade A), while AASLD encourages multidisciplinary consideration for biopsy in LR-4/LR-5 lesions to enable molecular analysis (Level III, Weak Recommendation). On the contrary, EASL is currently not endorsing biopsy until therapeutic decisions can be reliably informed by molecular analysis (Level III, Strong Recommendation).[19–21]

Staging and treatment overview

The most widely used staging system and treatment strategy is the Barcelona Clinic Liver Cancer (BCLC) staging system, which classifies patients into five stages (BCLC 0-D) according to tumour burden, liver dysfunction, and performance status, each with a distinct natural history and treatment allocation (Fig. 4).[1,55] Patients diagnosed at very early or early stages may be eligible for curative therapies, including resection, liver transplantation (LT) based on Milan criteria (MC), or local ablation.[1] In the context of organ scarcity, a sequential approach with resection or ablation followed by salvage LT at recurrence within MC is endorsed by international guidelines as an effective strategy for selected transplantable patients with HCC.[19,20] Downstaging of intermediate-stage HCC to meet the MC is widely accepted.[56] Median OS with these therapies ranges from 60-70 months (resection, ablation) to 10 years (LT) (Table 2).[16,56,57] Intermediate stages (BCLC-B) typically present with asymptomatic multinodular, liver-confined disease and are treated with transarterial therapies such as transarterial chemoembolization (TACE), which yields a mOS of 26-30 months, or alternatively, transarterial radioembolization (TARE).[57,58] Two recent pivotal phase III trials demonstrated improved progression-free survival (PFS) with the combination of systemic immunotherapy-based regimens and TACE *vs.* TACE alone. Final adoption by guidelines is pending more mature OS data (Table 2).[59,60] Patients at this stage may also be considered for LT if downstaging is successful, or for systemic therapies if they progress or present contraindications to local therapies or if the tumour is infiltrative, diffuse, or extensive.

Patients at advanced stages (with either portal vein invasion, extrahepatic disease or ECOG performance status 1-2) are candidates for systemic therapies.[19–21] Approximately 50-60% of patients with HCC will ultimately be exposed to systemic therapies because they are diagnosed at advanced stages or they progress after surgical or locoregional

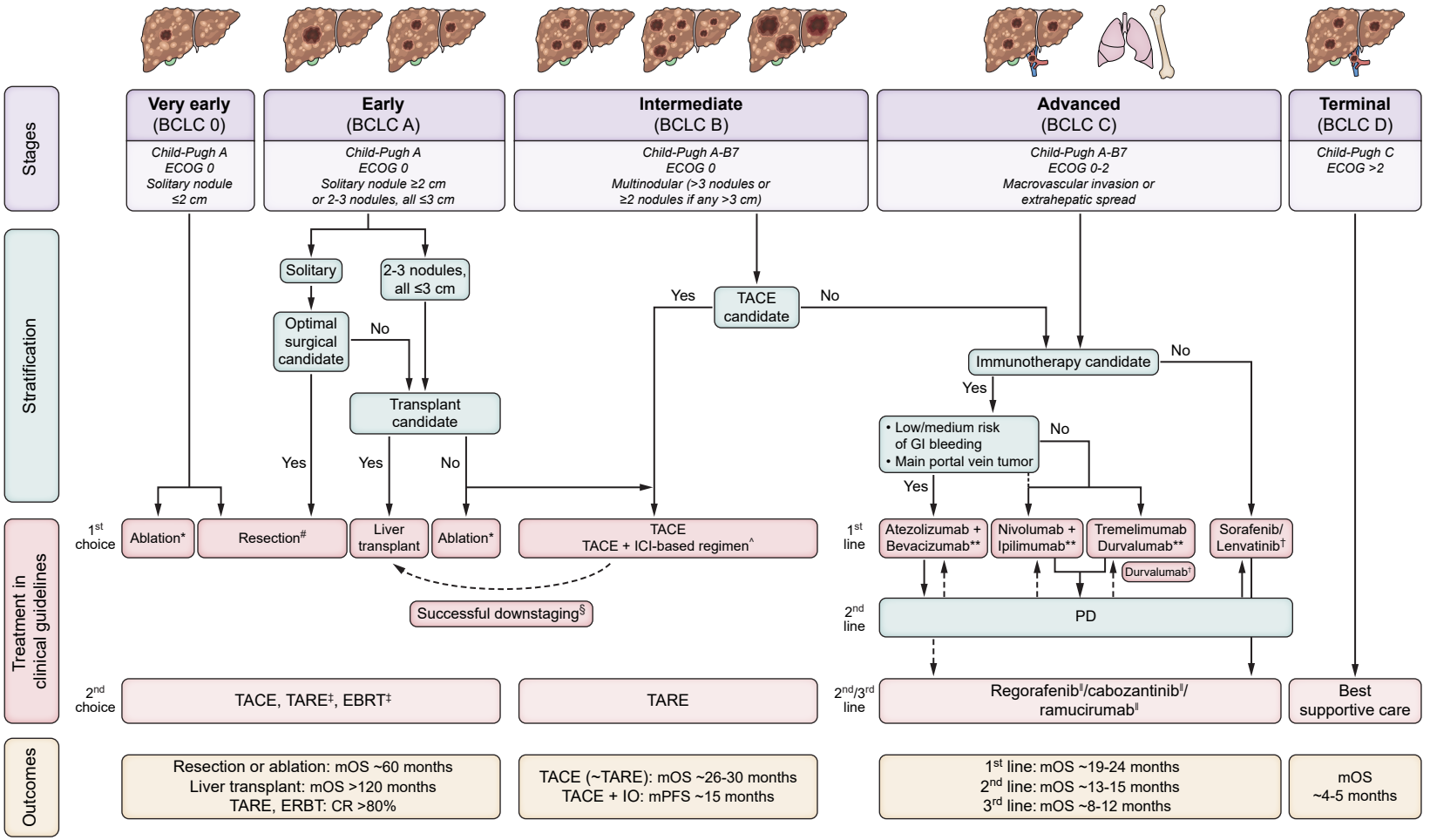


Fig. 4. Staging system and therapeutic strategy. The BCLC classification consists of five stages that identify the best candidates for therapies based on the level of evidence, prioritizing treatments that have demonstrated a survival benefit as the first option. *For patients without evidence of CSPH or minor degree of CSPH (≤12 mmHg) and resections involving fewer than 3 segments. If the patient has CSPH and requires major resection, consider LT. #Ablation (radiofrequency or microwave) has shown equal efficacy to resection in lesion <3 cm, surgery allows the assessment of histological predictors of recurrence, which can prioritise the indication for LT *ab initio*. Ablation is also an applicable method for multifocal BCLC A patients who are not candidates for LT. ‡Single lesions less than 8 cm §According to locally established criteria. ^Pending adoption in clinical practice guidelines, contingent on mature overall survival data. ⁱIn patients who achieve a significant objective response, the possibility of conversion therapy (surgery, liver transplantation, or locoregional treatment) may be considered. **These treatments demonstrated a benefit in OS compared to sorafenib or lenvatinib. In cases of sustained complete response to immunotherapy-based treatment, stage migration to curative therapies (resection or LT) may be considered on an individual basis. †These treatments demonstrated non-inferiority compared to sorafenib. Solid arrows indicate treatments for which there is clear evidence; dotted arrows indicate treatments in the second/third line for which further studies are required. ‖OS benefit demonstrated after sorafenib in RCT phase III. ‖‖IO treatments available in China for first-line: camrelizumab + rivoceranib** (CARES-310 trial); sintilimab + IBI305** (ORIENT-332 trial), anlotinib + penpulimab** (APOLLO trial), tislelizumab† (RATIONALE-301 trial). In second-line: pembrolizumab (KEYNOTE-240 trial). BCLC, Barcelona Clinic Liver Cancer; CR, complete response; Durva, durvalumab; EBRT, external beam radiation therapy; ECOG, Eastern Cooperative Oncology Group performance status; GI, gastrointestinal; IO, immuno-oncology; Lenva, lenvatinib; LT, liver transplantation; mOS, median overall survival; mPFS, median progression-free survival; mTTP, median time to progression; Pembro, pembrolizumab; RCT, randomised controlled trial; TACE, transcatheter arterial chemoembolisation; TARE, transcatheter arterial radioembolisation.

Table 2. Summary of current standard-of-care therapies and outcomes.

Clinical eligibility criteria and/or line of therapy	Treatment	Outcomes	Level of evidence & Recommendation (AASLD – EASL – ESMO)[19–21]
Very early (BCLC 0)			
Single tumour <2 cm in diameter[87]	Local ablation or resection	OS >70% at 5 yrs, ORR ∼95-100%	AASLD: I/II – Strong EASL/ESMO: II – Strong ESMO: II – Strong
Early (BCLC A)			
Single tumour and preserved liver function[# 69]	Resection	OS ∼60-70% at 5 years, mRFS ∼40-50 months Perioperative mortality <2%	AASLD/EASL/ESMO: II – Strong
≤3 nodules and ≤3 cm, with preserved liver function[88] Single tumour >5 cm, multifocal, and Vp1/Vp2[68]	Local ablation (RFA or MWA) Resection	OS ∼60-70% at 5 years, RFS ∼43-70% at 5 years OS ∼40-50% at 5 years, mRFS ∼20-30 months Perioperative mortality <10%	AASLD/EASL/ESMO: II – Strong AASLD/EASL: III – Weak ESMO: II – Strong
Milan criteria[56,77,78,80]	Liver transplantation	70-80% at 5 years, Recurrence rate <10% at 5 years	AASLD/EASL/ESMO: II – Strong
Downstaging to Milan criteria.[56,78]	Liver transplantation	60-80% at 5 years, Recurrence rate ∼20% at 5 years	AASLD/ESMO: II – StrongESMO: III – Moderate
Single tumour (median ∼3 cm)[93,94]	TARE (radiation segmentectomy)	mOS >5 years, ORR* ∼80%	AASLD: III – Strong EASL: III – Weak ESMO: III – Moderate
Single tumour <3 cm in diameter or 2 nodules each <3 cm[89]	External beam radiation therapy (PBT or SBRT)	mOS >5 years, Local PFS at 2 years: 93%	AASLD: III – StrongEASL: III – WeakESMO: III – Moderate
Intermediate (BCLC B)			
Multinodular without vascular invasion[90]	TACE	mOS ∼30 months, ORR* ∼50-60%, Treatment-related mortality <1%	AASLD/EASL: I – Strong ESMO: I – Moderate
Multinodular without vascular invasion[95]	TARE	mOS ∼30 months, ORR* ∼30-70%	AASLD: III – Strong EASL: III – Weak ESMO: II – Moderate
Multinodular without vascular invasion, ECOG 0-1[62]	TACE + pembrolizumab + lenvatinib	mPFS 14.7 months, ORR* 47% ORR** 72%	AASLD/EASL: NA ESMO: I – Weak
Multinodular, ECOG 0-1, and Vp1/Vp2[59]	TACE + durvalumab + bevacizumab	mPFS 15 months, ORR* 44% ORR** 58%	AASLD/EASL: NA ESMO: I – Weak
Advanced (BCLC C) 1st line			
Child-Pugh A ECOG 0-1BCLC B/C (18%/82%). Including Vp4[98]	Atezolizumab 1,200 mg + bevacizumab 15 mg/kg Q3W	mOS 19.2 (17.0-23.7) HR OS 0.66 (0.52-0.85) mPFS 6.9 (5.7-8.6) ORR* 29.8% DoR 18.1 months	AASLD/EASL/ESMO: I – Strong
Child-Pugh A ECOG 0-1BCLC B/C (19%/81%)[7]	Durvalumab 1,500 mg Q4W + tremelimumab 300 mg single dose (STRIDE)	mOS 16.4 (14.2-19.6) HR 0.78 (0.65-0.93) mPFS 3.78 (3.7-5.3) ORR* 20.1% DoR 22.3 months	AASLD/EASL/ESMO: I – Strong
Child-Pugh A ECOG 0-1BCLC B/C (27%/73%)[8]	Nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W (up to 4 cycles)	mOS 23.7 (18.8-29.4) HR 0.79 (0.65–0.96) mPFS 9.1 (6.6-10.5) ORR* 36% DoR 30.4 months	AASLD/EASL/ESMO: I – Strong
Child-Pugh A ECOG 0-2BCLC B/C (18%/82%) Including Vp4[61]	Sorafenib 800 mg	mOS 10.7 (9.4-13.3) HR 0.69 (0.55-0.87) ORR* 2%	AASLD/EASL/ESMO: I – Strong

(*continued on next page*)

Table 2. (*continued*)

Clinical eligibility criteria and/or line of therapy	Treatment	Outcomes	Level of evidence & Recommendation (AASLD – EASL – ESMO)[19–21]
Child-Pugh A ECOG 0-1BCLC B/C (21%/79%)[62]	Lenvatinib 8/12 mg	mOS 13.6 (12.1-14.9) HR 0.92 (0.79-1.06) mPFS 7.4 (6.9–8.8) ORR* 19% DoR 12.6 months	AASLD/EASL/ESMO: I – Strong
Advanced (BCLC C) 2nd line			
Child-Pugh A ECOG 0-1BCLC B/C (13%/87%) Sorafenib tolerant[63]	Regorafenib 160 mg (ON-OFF)	mOS 10.6 (3.1-12.1) HR 0.63 (0.50–0.79) mPFS 3.1 (2.8-4.2)§ ORR** 11% DoR 3.2 months	AASLD/EASL/ESMO: I – Strong
ECOG 0-1BCLC B/C (9%/91%) 2nd/3rd lines[64]	Cabozantinib 60 mg	mOS 10.2 (9.1-12.0) HR 0.76 (0.63-0.92) mPFS 5.2 (4.0–5.5)§ ORR** 4% DoR 5.5 months	AASLD: I – Strong EASL: I – Strong ESMO: I – Strong
Child Pugh A ECOG 0-1BCLC B/C (19%/81%) AFP ≥400 ng/ml[65]	Ramucirumab 8 mg/kg Q2W	mOS 8.5 (7.0–10.6) HR 0.71 (0.53-0.95) mPFS 2.8 (2.8-4.1)§ ORR** 5% DoR 4.6 months	AASLD/EASL/ESMO: I – Strong
Child-Pugh A ECOG 0-1BCLC B/C (7%/93%)[107]	Pembrolizumab 200 mg Q3W	mOS 14.6 (12.6-18) HR 0.79 (0.63-0.99) mPFS 2.6 (1.5-2.8) ORR* 13.7% DoR 23.9 months	AASLD: NA EASL: NA ESMO: NA

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CSPH, clinically significant portal hypertension; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; mPVI, main portal vein invasion; mRFS, median recurrence-free survival; ORR, objective response rate; PBT, proton beam therapy; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation.
#Child-Pugh A and without CSPH or minor CSPH.
§By mRECIST.
*RECIST 1.1.
**mRECIST.

therapies. Immunotherapy-based regimens, including atezolizumab-bevacizumab, durvalumab-tremelimumab, and nivolumab-ipilimumab, are superior to single tyrosine kinase inhibitor (TKI) regimens and are accepted as the standard of care.[6–8] However, for patients with contraindications to immunotherapies, sorafenib[61] and lenvatinib[62] remain first-line options. Those who progress on or fail these first-line therapies may receive an alternative first-line agent with a different mechanism of action or single-agent drugs that have shown superiority to placebo after progression on sorafenib, such as regorafenib,[63] cabozantinib,[64] and ramucirumab (in patients with AFP >400 ng/ml).[65] Finally, patients with end-stage disease should receive nutritional and psychological support and pain management (Fig. 4).[19–21] Given the complexities of HCC diagnosis and treatment, referral to centres with multidisciplinary liver cancer programmes is recommended.[19–21]

Surgical treatments

Surgical interventions, such as liver resection and LT, are the cornerstone of treatment for early HCC, leading to long-term cancer-free survival, with estimated rates of ∼30% for liver resection and ∼85% for LT (Table 2).[19–21]

Liver resection

Partial hepatectomy is the treatment of choice for patients with HCC and no underlying cirrhosis given the minimal risk of postoperative hepatic decompensation. In patients with cirrhosis, Western guidelines recommend surgical resection for those with a single tumour (regardless of size), well-preserved liver function (Child-Pugh A, total bilirubin <1 mg/dl), and no clinically significant portal hypertension (hepatic venous pressure gradient [HVPG] <10 mmHg).[19,20] In clinical practice, direct HVPG measurement is not always available, so surrogate markers such as platelet counts (>100,000/μl), absence of splenomegaly, and no portosystemic collaterals, are often used.[19,20] Adherence to these criteria yields 5-year survival rates of ∼70% and a perioperative mortality <3%. Minor resections (<3 liver segments) may remain feasible in mild portal hypertension (HVPG ≤12 mmHg), provided that the estimated risk of decompensation remains <30%.[19,20] Surgical selection also integrates MELD or Child-Pugh/ALBI scores for the stratification of liver function, future liver remnant volumetry, and comorbidity review.[19,20] Although evidence is limited, resection may yield better outcomes than locoregional therapies in patients with multifocal HCC (≤3 nodules <3 cm) when surgery is feasible; however, current data are insufficient to favour one approach over the other.[20,66] In this setting, minimally invasive approaches (laparoscopic or robotic-assisted resections) were associated with improved perioperative outcomes compared to open surgery.[67] Beyond these limits, resection is precluded according to Western guidelines but accepted in Asian studies.[19,20,68]

From an oncological standpoint, HCC recurrence occurs in 50-70% of cases after 5 years, even in the most favourable series.[69] HCC recurrence often follows a bimodal pattern: an early peak (~1 year), driven by true metastases and a potential target for adjuvant systemic therapies, and a later peak (~4 years) for *de novo* metachronous tumours. While this framework is conceptually useful, the underlying mechanisms may overlap, and both types of recurrence can only be characterised through molecular analyses.[70–73] Neoadjuvant and adjuvant therapies remain an unmet need.[16,74] Although adjuvant atezolizumab plus bevacizumab showed initial promise, it did not yield sustained improvements in recurrence-free survival upon extended follow-up.[75,76] Ongoing phase III adjuvant studies also face the challenge of defining high-risk populations, ranging from multinodular tumours up to 10 cm to Vp1-2 macrovascular invasion, which complicates their interpretation and applicability.[16]

Liver transplantation

LT is recognised as the main surgical treatment for patients with HCC and cirrhosis who satisfy the MC, defined as a single tumour ≤5 cm, or up to three tumours each ≤3 cm, particularly in the context of liver dysfunction (Child-Pugh B or C).[19–21] LT offers the most significant survival benefit in HCC due to its ability to eliminate both the tumour and the underlying chronic liver disease. Nevertheless, the scarcity of donor organs continues to be a significant barrier to widespread application, underscoring the necessity for refined patient selection criteria.[1,19,20] The MC set a validated benchmark for identifying ideal candidates for LT, with a predicted post-LT survival rate exceeding 70% at 5 years (Table 2).[77] The expansion of the MC to "extended" criteria and the practice of tumour downstaging to within the MC have been adopted globally.[19,56,78] Overall, outcomes are improved in high-volume centres, with the current benchmark being a mOS of more than 10 years.[19,56] Tumour biology, and the risk of post-LT recurrence, is largely reflected by pre-LT AFP levels, the extent of response to locoregional therapies, and pathological findings on the explant (for example, vascular invasion).[19,20,79] Several models reported an accurate prediction of survival, and the best performance has been assigned to the Metroticket 2.0 and the AFP-French model.[80,81]

Several strategies have improved the allocation of resources with an expected impact on outcomes in LT: living donors, the use of *ex vivo* perfusion machines for reconditioning of suboptimal organs, and the use of neoadjuvant immune-based regimens along with locoregional therapies.[82–84] A recent study exploring neoadjuvant immunotherapies demonstrated promising intention-to-treat survival, safety, and rejection outcomes, particularly in high-risk patients with elevated AFP.[85] Meanwhile, a recent review of 90 cases demonstrated the efficacy of these regimens (rejection risk of ≤20%) if the washout period was ~3 months, providing a proof of concept to test these approaches in the setting of prospective studies.[86]

Locoregional treatments

Locoregional therapies for HCC include local ablation, TACE, and TARE. Locoregional therapy typically serves the following purposes: curative intent or bridging to LT at early stages, downstaging to LT, and primary treatment at intermediate stages (Fig. 4).[57]

Local ablation and external beam radiation therapy

Thermal ablation, typically by radiofrequency ablation (RFA) or microwave ablation (MWA), is a first-line curative strategy for very early HCC (BCLC 0).[19–21] Both produce outcomes comparable to surgical resection in patients with compensated cirrhosis and tumours ≤3 cm.[87] RFA remains the most widely used and consistently achieves complete response rates higher than 90% with a median overall survival of ~60 months, though 5-year recurrence can reach 43-70%.[57,88] MWA delivers higher power and creates larger ablation zones (potentially up to 4 cm), allowing simultaneous multi-probe use.[57] Although meta-analyses suggest similar efficacy for RFA and MWA, MWA may offer a slight advantage in tumours >3 cm but is associated with higher complication rates.[57] For BCLC A cases unfit for surgery, both RFA and MWA are recognised as effective modalities, with treatment choice depending on tumour characteristics and location, operator expertise, and local resources (Table 2).[19–21] External beam radiation therapy has recently been adopted with a moderate recommendation by Western guidelines as an alternative to RFA for the treatment of early HCC based on a small randomised controlled trial (RCT).[19,20,89]

Transarterial therapies

TACE is the standard of care for intermediate-stage HCC based on two phase III trials demonstrating a survival benefit over best supportive care or suboptimal treatments,[90,91] corroborated by a subsequent meta-analysis.[92] Notably, guidelines recommend TACE in case of treatment stage migration for patients with early-stage disease when surgical or ablative therapies are unfeasible (Fig. 4).[19–21]

TACE comprises conventional TACE, which is an emulsification of lipiodol (a radio-opaque oil) and a drug (most commonly doxorubicin), or drug-eluting bead TACE.[57] The goal is to saturate the tumour with a high drug concentration and then occlude the vessels, leading to hypoxia.[57] Superselective TACE mitigates ischaemic damage to non-tumoral parenchyma.[19] ESMO and EASL guidelines, but not AASLD guidelines, propose bland embolisation (TAE) as an alternative to TACE.[19–21]

TACE is only feasible in ~50% of patients with BCLC B disease, largely owing to factors such as liver dysfunction (ascites or encephalopathy), technical contraindications (for example, impaired portal vein flow), or excessive tumour burden (main tumour size >10 cm).[57] The combination of TACE with TKIs did not result in improved outcomes, but helped to establish modern benchmarks for median OS (26-30 months), PFS (8 months) and objective response (~50-60% as per mRECIST).[57] Two recent trials combining TACE with durvalumab-bevacizumab (EMERALD-1)[59] or with lenvatinib-pembrolizumab (LEAP 012)[60] resulted in significant benefits in PFS, with the latter also showing a trend towards better OS (Table 2). Adoption by guidelines is pending more mature OS data.

TARE is a radiation-based treatment that employs Yttrium-90 as the radioisotope. TARE rarely causes occlusion of targeted vessels and seeds the neoplastic tissue with 40 μm

spheres embedded with Yttrium-90.[57] With radiation segmentectomy, Yttrium-90 spheres are delivered selectively to achieve a tumoricidal dose to the tumour with a surrounding treatment margin to the perfused region, while sparing the non-tumoral parenchyma.[93,94] Studies have reported an 84–90% complete response rate per mRECIST for solitary lesions up to 8 cm when using a 400-Gy dose threshold, with few grade 3–4 toxicities.[93,94] These findings contributed to FDA approval of TARE, now incorporated into BCLC early-stage treatment for curative intent and into bridging/down-staging protocols before LT (Fig. 4, Table 2). However, in the LEGACY study, the median tumour size was 2.6 cm, which should be considered when interpreting the generalisability of these results to larger lesions.[94] While no phase III trials have directly compared TACE and TARE, TARE has emerged as an alternative to TACE in patients with intermediate-stage HCC, supported by evidence from a phase II study (Table 2).[19,95] In the United States, TARE, particularly using a radio-segmentectomy approach, has become the most commonly used locoregional therapy in LT candidates.[96] This shift reflects both the favourable safety profile and the growing evidence of efficacy in well-selected patients. The combination of TARE with immunotherapy has shown a favourable safety profile,[97] whether tested in the neoadjuvant setting for LT (atezolizumab and bevacizumab in combination with TARE, NCT07059494) or as primary treatment for intermediate HCC (EMERALD-Y90 [NCT06040099]: durvalumab and bevacizumab after TARE; and ROWAN [NCT05063565]: durvalumab with tremelimumab after TARE).

Systemic therapies

First-line systemic treatment strategies

Immunotherapy has become the cornerstone of systemic treatment for HCC, particularly for intermediate HCC cases who are not candidates for or who have progressed on TACE, as well as for those with advanced disease.[19–21]

The combination of anti-PD-L1 plus anti-VEGF (atezolizumab plus bevacizumab) was the first to outperform sorafenib, demonstrating a median OS of 19.2 months *vs*. 13.4 months and an objective response rate (ORR) of 30% *vs.* 12%, with lower grade 3-4 toxicities than sorafenib.[6,98] Preemptive variceal screening and prophylaxis are mandatory to mitigate bevacizumab-related bleeding risk, particularly in the setting of main portal vein thrombosis (Vp4) (Table 2).[19–21]

Other immunotherapy-based doublets are also effective. A single dose of tremelimumab (anti-CTLA-4) plus monthly durvalumab (anti-PD-L1, the so-called STRIDE regimen) showed an mOS of 16.4 months compared to 13.8 months with sorafenib, with a 20% ORR and a 5-year survival rate of 19.6%.[7,99] This regimen may be preferable for patients at a higher risk of bleeding complications or cardiovascular events, which may contraindicate bevacizumab.[19–21] However, it is associated with a higher incidence of immune-mediated adverse events (irAES), which require systemic steroid treatment in approximately 20% of patients.[7,99] Another recently approved combination, nivolumab (anti-PD-1) plus ipilimumab (anti-CTL-4), was superior to either lenvatinib or sorafenib, with an mOS of 23.7 *vs.* 20.6 months, ORR of 36%, and a 3-year survival rate of 38%.[8] This regimen involved up to four cycles of CTLA-4 inhibition leading to ~30% of the patients requiring high-dose steroids (Table 2).[8]

TKIs remain a viable option for patients with contraindications to immunotherapy, such as active autoimmune disorders or prior organ transplantation.[19–21] Sorafenib[61] has historically demonstrated mOS rates of ~12-14[7] months and an ORR of ~5-11%,[6] with manageable adverse events. Recent data from LEAP-002 showed that lenvatinib led to mOS of 19 months, PFS of 8.1 months and an ORR of 17.5%,[100] also with manageable adverse events, supporting its role as the preferred first-line TKI.[62,100] Lenvatinib is more frequently associated with grade 3-4 hypertension and proteinuria, whereas sorafenib often presents more severe hand-foot skin reactions.[62] Several other regimens remain unapproved due to limited Western representation in clinical trials (CARES-310: camrelizumab + rivoceranib, ORIENT_332: sintilimab + IBI305, APOLLO: anlotinib + penpulimab, and RATIONALE-301: tislelizumab), lack of a clear therapeutic advantage, or manufacturing challenges.[101–104]

Finally, while emerging data suggest prolonged benefits of ICI-based regimens in patients with compensated cirrhosis (Child-Pugh A), definitive evidence in Child-Pugh B cirrhosis remains limited and controversial.[105] Current studies are being conducted to clarify the impact on survival in this high-risk subgroup.

Sequential strategy and second-line systemic treatment

Following the progression of a first-line ICI-based combination for advanced HCC, there are limited prospective data to guide the choice of subsequent therapy. The use of TKIs such as lenvatinib, sorafenib, cabozantinib, and regorafenib is supported by clinical practice guidelines[19–21] and by evidence of their efficacy either as first-line agents[61,62] or second-line following progression on sorafenib.[63–65] Ramucirumab, a VEGFR2-targeting monoclonal antibody, also extends survival in patients with elevated baseline AFP (≥400 ng/ml) who have progressed on sorafenib[65] and is recognised as another option (Table 2).[19–21] One small phase II trial evaluated patients refractory to prior ICI-based treatment who received cabozantinib as second- or third-line therapy. The mOS was ~9.9 months in the entire cohort and ~14.3 months when used in the second line.[106]

If a TKI is used initially, an ICI-based regimen can be considered in the absence of contraindications.[19,21] Pembrolizumab improved OS over placebo as monotherapy in a phase III study after sorafenib[107] and nivolumab-ipilimumab achieved a high ORR (~32%) after sorafenib. Retrospective data have also suggested potential efficacy of nivolumab-ipilimumab after prior atezolizumab-bevacizumab,[108] suggesting potential benefit. However, prospective evidence to guide optimal sequencing after a specific first-line ICI-based combination is currently lacking.

Innovative strategies and emerging therapies in advanced HCC

The treatment landscape for HCC is rapidly evolving. In early-stage disease, neoadjuvant and adjuvant therapies are expected to improve outcomes, as observed in melanoma and non-small cell lung cancer. In advanced HCC, new regimens that add a third agent, such as anti-TIGIT (recently reported

negative)[109] or anti-LAG3 antibodies, to existing ICI–ICI or ICI-VEGF combinations aim to deepen and prolong response rates. Personalised cancer vaccines targeting neoantigens may further enhance immune activation.[16,110] However, a significant proportion of patients exhibit primary resistance to ICIs due to an immunosuppressive tumour microenvironment. In these cases, blocking the immunosuppressive (WNT–β-catenin and TGF-β) or aggressive proliferative pathways (Notch) or using CAR (chimeric antigen receptor) technologies (CAR T cells and CAR macrophages) targeting HCC-specific antigens may offer alternative strategies.[111] These emerging strategies have significant potential to refine and expand treatment options for patients with advanced HCC.

Conclusions

HCC remains a major global health challenge, with incidence and mortality projected to rise further by 2045, largely due to shifting aetiologies, particularly the growing burden of MASLD and ALD. Preventive measures must adapt to these evolving risk factors, and more rigorous implementation of surveillance along with an improvement in its accuracy is urgently needed, given that less than one-third of patients are diagnosed at a stage where curative therapies are recommended. Although immunotherapy has nearly doubled survival in advanced disease to around 2 years, pressing challenges persist regarding optimal treatment sequencing and expanding the use of immunotherapy to the early and intermediate stages of disease. The expanding role of systemic therapies in the neoadjuvant and intermediate stage settings is increasingly recognised and holds the potential to reshape current therapeutic paradigms. Future priorities include validating reliable biomarkers for patient selection and developing more potent therapies to overcome immunotherapy resistance, ultimately enabling deeper and more durable responses.

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Abbreviations

AFP, alpha-fetoprotein; ALD, alcohol-related liver disease; ASR, age-standardised incidence rate; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; ICI, immune checkpoint inhibitor; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MC, Milan criteria; mOS, median overall survival; MWA, microwave ablation; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitor.

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Conflict of interest

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

Authors' contributions

EM and JM designed the review, coordinated the tasks, and provided critical input and final editing. TDC, MZ, MS, AV, and VM drafted specific sections. JML supervised the review. All authors approved the final version.

Supplementary data

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