VOLUME 31 SUPPLEMENT February 2025
pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

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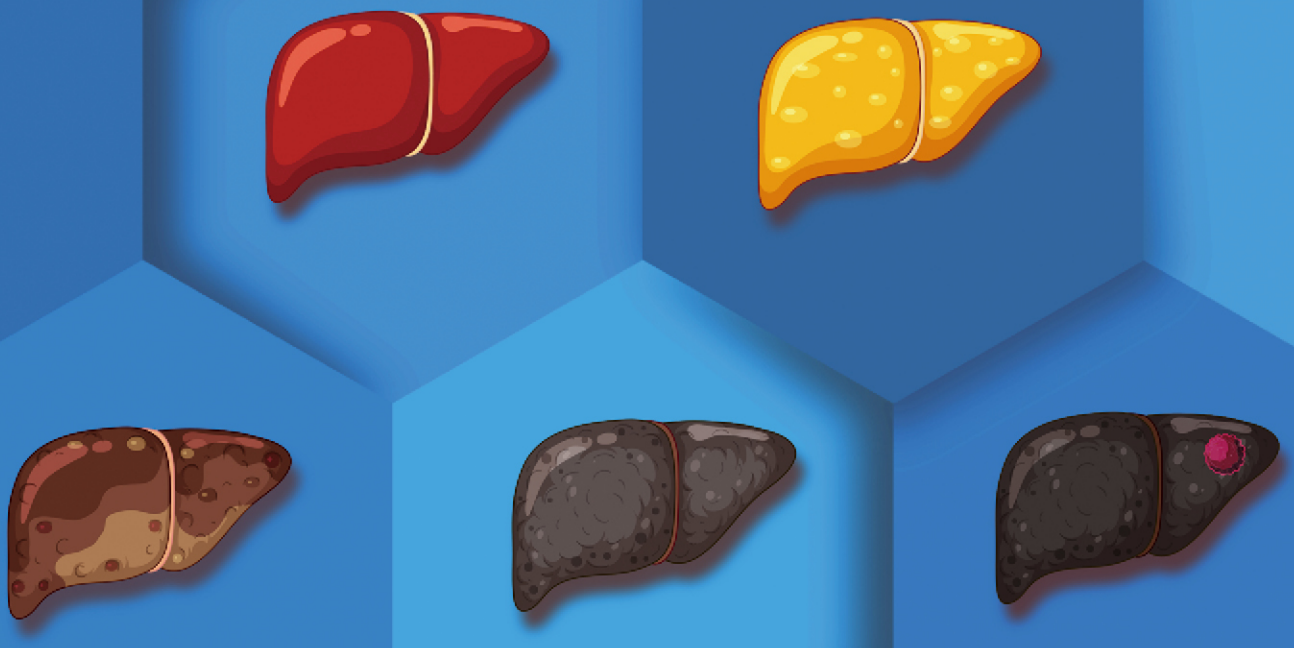

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pISSN 2287-2728
eISSN 2287-285X

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https://doi.org/10.3350/cmh.2024.0824
Clinical and Molecular Hepatology 2025;31(Suppl):S228-S254

Review

Hepatocellular carcinoma: updates on epidemiology, surveillance, diagnosis and treatment

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Hepatocellular carcinoma (HCC) is a major global burden, ranking as the third leading cause of cancer-related mortality. HCC due to chronic hepatitis B virus (HBV) or C virus (HCV) infection has decreased due to universal vaccination for HBV and effective antiviral therapy for both HBV and HCV, but HCC related to metabolic dysfunction-associated steatotic liver disease and alcohol-associated liver disease is increasing. Biannual liver ultrasonography and serum α-fetoprotein are the primary surveillance tools for early HCC detection among high-risk patients (e.g., cirrhosis, chronic HBV). Alternative surveillance tools such as blood-based biomarker panels and abbreviated magnetic resonance imaging (MRI) are being investigated. Multiphasic computed tomography or MRI is the standard for HCC diagnosis, but histological confirmation should be considered, especially when inconclusive findings are seen on cross-sectional imaging. Staging and treatment decisions are complex and should be made in multidisciplinary settings, incorporating multiple factors including tumor burden, degree of liver dysfunction, patient performance status, available expertise, and patient preferences. Early-stage HCC is best treated with curative options such as resection, ablation, or transplantation. For intermediate-stage disease, locoregional therapies are primarily recommended although systemic therapies may be preferred for patients with large intrahepatic tumor burden. In advanced-stage disease, immune checkpoint inhibitor-based therapy is the preferred treatment regimen. In this review article, we discuss the recent global epidemiology, risk factors, and HCC care continuum encompassing surveillance, diagnosis, staging, and treatments. **(Clin Mol Hepatol 2025;31(Suppl):S228-S254)**

Keywords: Hepatocellular carcinoma; Liver neoplasms; Liver diseases; Liver cirrhosis

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Editor: Ju Hyun Shim, University of Ulsan, Korea

Received: Sep. 22, 2024 / **Revised:** Nov. 8, 2024 / **Accepted:** Dec. 20, 2024

INTRODUCTION

Liver cancer is a global challenge, remaining among the leading cause of cancer-related death, with increasing mortality rates in many countries.[1] Hepatocellular carcinoma (HCC) is the most common form of liver cancer, accounting for around 90% of the cases.[2] The change in epidemiology has important implications for the optimal HCC prevention, screening, and treatment strategies. These implications are particularly important to consider in the context of emerging strategies for HCC screening (e.g., blood-based biomarker panels and abbreviated magnetic resonance imaging [MRI] protocols) and treatment (e.g., immune checkpoint inhibitors [ICIs] combinations). This review article aims to comprehensively review the current global epidemiology and state-of-the-art evidence in the surveillance, diagnosis, and treatment of HCC.

GLOBAL INCIDENCE AND MORTALITY OF HCC

Liver cancer ranks as the sixth most commonly diagnosed cancer and the third leading cause of cancer-related deaths worldwide.[1] According to the Global Burden of Disease (GBD) Study 2021, there were over 529,000 new cases and 483,800 deaths attributed to liver cancer in 2021.[3] In the past two decades, incidences of liver cancer increased by 53.7%, whereas death increased by 48.0% (Fig. 1A, 1B). The age-standardized incidence and death rates vary significantly by country (Fig. 1C, 1D),[4] with the highest incidence and mortality rates reported in Africa and the Western Pacific region. Liver cancer is predominantly diagnosed in middle-aged to older adults, with a median age of 62 at diagnosis; however, 14.7% of incident cases also occur in younger adults aged 15–49 years.[5-7] Despite improvements over time, the prognosis for liver cancer remains poor, with 5-year overall survival rates below 20%.[2,8]

The incidence of HCC varies globally due to the differing distribution of these risk factors.[9-12] According to GLOBOCAN 2020, over 70% of HCC cases occur in Asia, while Africa accounts for 7.8% of the global liver cancer burden, with hepatitis B virus (HBV) being the predominant risk factor in both regions. Europe contributes nearly 10% of the global HCC incidence, North America accounts for 5.1%, and South America represents 4.4%.[13,14] Despite these regional variations, there has been a notable shift in the etiology of HCC across most regions, transitioning from viral to non-viral etiologies.[15-18]

ETIOLOGY

Most patients diagnosed with HCC have underlying cirrhosis. Compared to patients without cirrhosis, those with cirrhosis face an over 30-fold increased risk of developing HCC.[19] The most common causes of liver cancer include metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-associated liver disease (ALD), chronic HBV infection, and chronic hepatitis C virus (HCV) infection, therefore making most HCC cases potentially preventable.[20] Less common causes include hereditary hemochromatosis, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, and aflatoxin exposure.[21-24] Over the past two decades, MASLD and ALD have been the only liver cancer etiologies with rising incidence rates.[3,4]

MASLD

According to GBD 2021 data, metabolic dysfunction-associated steatohepatitis (MASH)-associated liver cancer

Abbreviations:

AFB1, aflatoxin B1; AFP, alpha-fetoprotein; ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; AUC, area under the curve; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; CI, confidence interval; CT, computed tomography; DCP, des gamma carboxy prothrombin; DDLT, deceased donor liver transplantation; EV, extracellular vesicles; FDA, Food and Drug Administration; GBD, Global Burden of Disease; GALAD, gender, age, AFP-L3, AFP, des-gamma-carboxy prothrombin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HES, hepatocellular carcinoma early detection screening; HR, hazard ratio; ICI, immune checkpoint inhibitor; LDLT, living donor liver transplantation; LI-RADS, Liver Imaging Reporting and Data System; LT, liver transplantation; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MPR, major pathological response; MRI, magnetic resonance imaging; MWA, microwave ablation; NGS, next generation sequencing; RCT, randomized controlled trial; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitors; TTP, time to progression; UNOS, United Network for Organ Sharing; WHO, World Health Organization; Y90, yttrium-90

 https://doi.org/10.3350/cmh.2024.0824

made up 8% of all liver cancer cases and 9% of liver cancer-related deaths (Fig. 1E, 1F). Due to the rising prevalence of metabolic syndrome, MASH has become the fastest-growing cause of HCC in many regions of the world,[5,6,25,26] with disproportionate increases seen in low and low-middle-income countries.[27,28] MASLD is the most commonly occurring chronic liver disease, affecting one-fourth to one-third of the global population.[29-32] In addition to being a risk factor for chronic liver disease, MASLD can accelerate cardiovascular risk even in the absence of metabolic comorbidities.[33,34] Over time, hepatic steatosis causes a disruption in hepatic metabolism, increasing lipotoxicity and oxidative stress, and triggering immune system activation.[35] MASH, the inflammatory subtype of MASLD, involves both steatosis and signs of hepatocyte injury and inflammation.[36] It is currently estimated that approximately 25% of patients with MASLD progress to MASH.[37-39] Approximately 40% of MASH patients develop fibrosis, with 15% progressing to cirrhosis.[35] Interestingly, MASH-related HCC is more frequently observed in patients without cir-

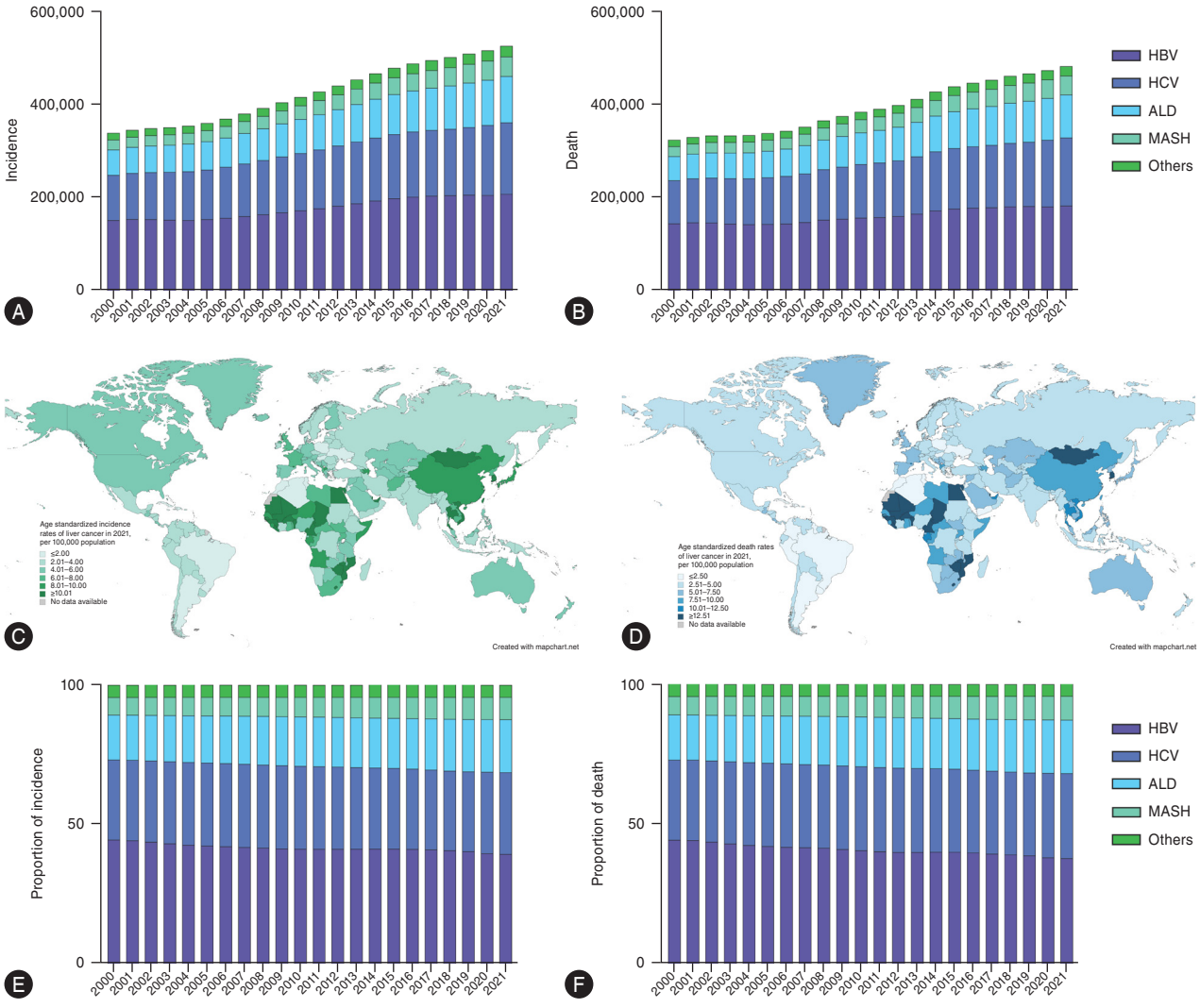

Figure 1. (A) Incidences attributable to liver cancer from 2000 to 2021, by etiology. (B) Deaths attributable to liver cancer from 2000 to 2021, by etiology. (C) Age-standardized incidence rates attributable to liver cancer in 2021 per 100,000 population by country. (D) Age-standardized death rates attributable to liver cancer in 2021 per 100,000 population by country. (E) Proportion of incidences of liver cancer attributable to different etiologies from 2000 to 2021. (F) Proportion of deaths from liver cancer attributable to different etiologies from 2000 to 2021. ALD, alcohol-associated liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; MASH, metabolic dysfunction-associated steatohepatitis.

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rhosis compared to HCC from other causes.[40] Emerging data also suggest that MASH-HCC patients may have distinct characteristics compared to those with HCC from other etiologies. Patients with MASH-HCC tend to be female and older and has more metabolic comorbidities.[41,42] Additionally, patients with MASH-HCC are often diagnosed at more advanced stages compared to HCC from other causes.[43,44]

Alcohol

In 2021, ALD-associated liver cancer represented 19% of both total liver cancer incidence and liver cancer-related deaths (Fig. 1E, 1F). The increase in global per-capita alcohol consumption has resulted in a surge in ALD and associated complications, particularly during the COVID-19 pandemic.[45-49] Another meta-analysis by the World Cancer Research Fund found that liver cancer risk increased by 4% for each 10 g of alcohol consumption per day.[50] A population-based study in Sweden, which utilized liver biopsy-proven ALD, found that patients with ALD had a significantly elevated risk of HCC, with a hazard ratio (HR) of 12.8 (vs. general population).[51] Another systematic review and meta-analysis of over 148,000 patients determined that the cumulative incidence of HCC in patients with ALD cirrhosis at 5- and 10-year follow-ups was 3% and 9%, respectively.[52] Alcohol-associated HCC is linked to more advanced Barcelona Clinic Liver Cancer (BCLC) staging at diagnosis, reduced chances of receiving curative treatment, and worse survival outcomes.[53] Chronic alcohol consumption also increases the risk of HCC in patients with other etiologies of chronic liver diseases.[54-57] Therefore, strict abstinence from alcohol is recommended in patients with chronic liver diseases to prevent the progression of liver diseases and ultimately, HCC development.

HBV

Chronic HBV infection was responsible for 39% of total liver cancer cases and 37% of liver cancer-related deaths (Fig. 1E, 1F). Patients with chronic HBV infection are at increased risk of developing HCC,[58] with risk significantly elevated by factors such as cirrhosis, high HBV DNA levels, specific genotypes, and co-infections (e.g., hepatitis D).[59-62] Although HBV remains the leading etiology of HCC globally, expanded vaccination coverage has led to a gradual decline in HBV-related HCC.[63] A recent study revealed a non-linear parabolic association between HBV DNA titer and HCC risk, with HBV DNA around 6 log10 IU/mL (moderate viral loads) corresponded to the highest non-invasive test scores for hepatic inflammation and fibrosis.[64,65] More recently, a large retrospective multinational study confirmed the nonlinear parabolic association between HBV DNA and HCC risk in patients with normal alanine aminotransferase (ALT).[65] Among patients with HBV infection, antiviral therapy, particularly with nucleos(t)ide analogs, significantly reduces HCC risk by 40–60% by suppressing viral replication and reducing inflammation, contributing to the global reduction of HBV-related HCC.[66-69]

HCV

Chronic HCV infection accounted for 29% of total liver cancer cases and 30% of liver cancer-related deaths (Fig. 1E, 1F). Chronic HCV infection is a well-established risk factor for HCC, with the highest risk observed in patients who have developed cirrhosis.[70] Increased implementation of HCV treatment programs using direct-acting antivirals has significantly reduced HCV-related HCC, although increased efforts are needed to meet World Health Organization (WHO) viral hepatitis elimination goals.[71-74] Further, HCC risk is significantly reduced but not eliminated after viral eradication, with studies showing persistent annual HCC incidence rates exceeding 1% more than 5 years after sustained virologic response, underscoring the importance of ongoing surveillance.[75-77]

Aflatoxin

Aflatoxins are potent carcinogenic mycotoxins that commonly contaminate foods such as maize and groundnuts, exposing approximately 4.5 billion people globally.[78,79] The majority of liver cancer cases linked to aflatoxin exposure are concentrated in Sub-Saharan Africa, Southeast Asia, and China.[80,81] The primary aflatoxin involved in liver carcinogenesis is aflatoxin B1 (AFB1), produced by Aspergillus species. AFB1 leads to the formation of DNA adducts, which interact with guanine bases in hepatocyte DNA, causing a mutation in the P53 tumor suppressor gene at the codon 249 hotspot in exon 7, ultimately resulting in

HCC.[82,83] The risk of HCC from aflatoxin is not evenly distributed, with a higher risk observed in children and individuals with HBV infection.[80,84] The increased risk observed with aflatoxin and HBV may be due to chronic HBV infection-inducing cytochrome P450 enzymes, which convert inactive AFB1 into the mutagenic AFB1–8,9-epoxide, thereby causing mutations in hepatocytes and ultimately hepatocarcinogenesis.[85]

SURVEILLANCE

Target populations

Current guidelines recommend semi-annual HCC surveillance in at-risk populations.[86-88] Traditionally, surveillance was deemed cost-effective in cirrhosis patients with an annual HCC incidence rate of 1.5% or greater.[89] More recent cost-effectiveness analyses demonstrated an HCC incidence of more than 0.4% per year and surveillance adherence of more than 19.5% biannually for ultrasound (US) with alpha-fetoprotein (AFP) to be cost-effective in patients with compensated cirrhosis.[90] Cirrhosis patients with Child-Pugh class A or B, regardless of etiology, should undergo surveillance, while this should be restricted to transplant-eligible patients in the setting of Child-Pugh class C cirrhosis.[86,91] Non-cirrhotic, chronic hepatitis B patients are also at high risk to warrant surveillance based on their risk factors such as age, sex, endemic region, family history, HBV DNA titer, or the PAGE-B score.[86] Although 25–30% of HCC cases in patients with MASLD occur in the absence of cirrhosis, the annual risk of HCC in noncirrhotic MASLD is low. Universal HCC surveillance is not cost-effective, underscoring the need for risk stratification in this patient population.[40] Precision surveillance based on risk group using four patient factors (sex, etiology of liver disease, Child-Pugh class, and body mass index) was able to detect a higher proportion of HCC at an early stage and was more cost-effective than the universal approach, although it requires further validation before implementation in clinical practice.[92]

Benefits and risks of HCC surveillance

The best data for HCC surveillance comes from a large randomized controlled trial (RCT) in patients with chronic HBV infection.[93] Although there is not a similar RCT among patients with cirrhosis, several cohort studies show associations between HCC surveillance and early-stage HCC detection, curative treatment receipt, and prolonged survival.[94] The benefits of HCC surveillance must be weighed against potential physical, psychological, and financial harms. There are fewer studies enumerating surveillance-related harms, although available data suggest these are of mild severity in most patients.[94-98] The balance of benefits vs. harms may be particularly relevant when expanding surveillance to patients with advanced fibrosis but no cirrhosis, in whom the annual incidence of HCC is lower, and the number needed to screen will inevitably become larger, further escalating the extent of unnecessary harm.[99,100]

Implementation and disparity of HCC surveillance

Despite the advancement in surveillance modalities for early HCC detection, HCC surveillance in clinical practice is underused. Among 1,014 patients with cirrhosis with HCC, only 37.2% of the patients had regular outpatient care the year before HCC presentation, and only 24.7% of those under regular outpatient care were under surveillance. Nearly half lacked surveillance orders despite knowing the patient had cirrhosis.[101] Underuse of HCC surveillance is related to a combination of patient and provider-reported barriers.[102,103] Common patient-reported barriers include cost, difficulty scheduling, uncertainty of where to receive an ultrasound exam, or difficulty with transportation.[102] Underuse of surveillance is particularly high in patients with non-viral liver diseases, including those with ALD or MASLD, related to a combination of difficulty recognizing at-risk patients as well as increased social and financial barriers.[53,104] HCC surveillance is also underused in racial and ethnic minorities, populations disproportionately impacted by HCC mortality.[105] Several interventions are efficacious in increasing surveillance, but studies are needed to see their effectiveness when implemented in routine clinical practice.[106]

Modality of surveillance

Biannual surveillance for HCC using abdominal ultra-

https://doi.org/10.3350/cmh.2024.0824

sound with/without AFP is recommended by multiple professional society guidelines with few notable similarities and differences (Table 1).[86-88,107] Biannual ultrasound has been the standard imaging of choice due to its cost-effectiveness, low risk of adverse events, and detection of other complications of cirrhosis.[87] However, the sensitivity of ultrasound for early-stage HCC is operator-dependent as well as varies widely based on the patient's body habitus, liver disease etiology, and presence of cirrhosis (Table 2).[108-110] Therefore, there are concerns that ultrasound performance will worsen over time given the shift from viral-related liver disease to increasing proportions due to MASLD and ALD. Although ultrasound in combination with AFP increases sensitivity for early-stage HCC detection, this strategy still misses over one-third of HCC at an early stage.[90]

There are multiple emerging blood- and imaging-based strategies for HCC surveillance (Table 2). AFP-L3, which measures a subfraction of the AFP, and des gamma carboxy prothrombin (DCP), also known as protein induced by

Table 1. Summary of surveillance tools recommended for hepatocellular carcinoma based on international society guidelines

Surveillance recommendation	European Association for the Study of the Liver (EASL) 2018[87]	American Association for the Study of Liver Diseases (AASLD) 2023[86]	Asian Pacific Association for the Study of the Liver (APASL) 2017[88]
Indication for surveillance	- Cirrhotic patients, Child-Pugh stage A-B or Child-Pugh stage C waiting transplantation - Non-cirrhotic HBV patients at intermediate (PAGE-B 10-17) or high risk of HCC (PAGE-B ≥18) (for Caucasians) - Non-cirrhotic F3 patients considered for surveillance based on individual risk assessment Patients on waiting list for transplantation to detect, manage tumour occurrence/response, and help define priority policies for transplantation (Strong Recommendation) Role for NAFLD without cirrhosis unclear	- Child-Pugh A-B cirrhosis, any etiology - Child-Pugh C cirrhosis, transplant candidate - Non-cirrhotic chronic hepatitis B: Males aged >40 yr from endemic country Females aged >50 yr from endemic country Person from Africa at earlier age Family history of HCC PAGE-B score ≥10 - Need of risk stratification: hepatitis C and stage 3 fibrosis, noncirrhotic NAFLD Patients listed for transplantation should undergo HCC surveillance (Strong Recommendation)	- Cirrhotic hepatitis patients, any etiology - Chronic HBV carriers, non-cirrhotic (HBsAg positive): Asian females >50 yr Asian males >40 yr Africans aged >20 yr History of HCC in family
Surveillance interval	Every 6 mo		
Surveillance modality	- Abdominal ultrasound by experienced personnel (Strong Recommendation) - Multidetector CT or dynamic MRI are not cost-effective has high false-positive results in general, but might be considered in listed patients for liver transplant or inadequate US assessment (e.g., obesity, intestinal gas) - Tumour biomarkers for accurate early detection still lacking. Biomarkers tested (i.e., AFP, AFP-L3 and DCP) are suboptimal in terms of cost-effectiveness for routine surveillance of early HCC	- Ultrasound and AFP (Strong Recommendation) - Do not recommend routine use of CT/MRI-based imaging and tumor biomarkers, outside of AFP (Weak Recommendation) - Alternative imaging modalities, such as contrast-enhanced MRI, may be considered in select patients in whom US-based surveillance is suboptimal (Weak Recommendation)	- Combination of US and serum AFP (Weaker Recommendation) - AFP alone is not recommended for routine surveillance (Strong Recommendation) - Cut-off value of AFP should be set at 200 ng/mL when used in combination with US. It can be set at lower value in a population with hepatitis virus suppression/eradication (Weaker Recommendation)

AFP, alpha-fetoprotein; CT, computed tomography; DCP, des gamma carboxy prothrombin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; US, ultrasound.

vitamin K absence/antagonist-II (PIVKA-II) are two serum protein biomarkers extensively studied and currently approved by the Food and Drug Administration (FDA) for risk stratification.[111] Although each biomarker has insufficient sensitivity for early-stage when used alone, biomarker panels including multiple biomarkers appear to have higher accuracy. The original hepatocellular carcinoma early detection screening (HES) score combining AFP with age, ALT, and platelet count has shown to be superior to AFP alone for detection of early HCC, and a more recent version of HES V2.0 including AFP-L3 and des-gamma-carboxy prothrombin was proposed with excellent performance.[112,113]

The GALAD (gender, age, AFP-L3, AFP, des-gamma-carboxy prothrombin) model combined the three biomarkers and was recently evaluated in a national phase 3 biomarker study demonstrating an increase in accuracy: GALAD had the highest true positive rate (63.6%, 73.8%, and 71.4% for all HCC, and 53.8%, 63.3%, and 61.8% for early HCC within 6, 12, and 24 months, respectively).[111,114,115] Another phase 3 study revealed that longitudinal GALAD further improved the sensitivity up to 66.7% (vs. 54.8% for single point GALAD).[116] Given these promising results, GALAD is now undergoing prospective validation compared to ultrasound in a large RCT in the US enrolling over 5,000 pa-

Table 2. Summary of the accuracy of surveillance tools for hepatocellular carcinoma

Surveillance tools	Sensitivity	Specificity	Comments
Ultrasound (US)[110]	27.9–100% (all HCC) 21.4–68.2% (early-stage HCC)	70.7–99.6% (all HCC) 89.7–96.2% (early-stage HCC)	· Pooled sensitivities for all HCC 84% (95% CI 76–92%) · Pooled sensitivities for early-stage HCC 45% (95% CI 30–62%)
US plus AFP[110]	32.6–100% (early-stage HCC)	82.7–88.2% (early-stage HCC)	· Pooled sensitivities for early-stage HCC 63% (95% CI 48–75%)
AFP-L3%[111]	62%	90%	
DCP[111]	40%	81%	
GALAD model[111]	62.9–73.3% (all HCC) 51.9–62.5% (early-stage HCC)	90%	· Including gender, age, AFP-L3, AFP, des-gamma-carboxy prothrombin · Phase 3 biomarker study
Hepatocellular carcinoma early detection screening (HES) algorithm V2.0[112,113]	47.2% (any time before HCC diagnosis)	90.0% (fixed FPR of 10%)	· Age, etiology, AFP, ALT, platelet included in HES V1.0 and in addition AFP-L3 and des-gamma-carboxy prothrombin included in HES V2.0 · AUROC for any HCC and early-stage HCC at any time is 0.77 and 0.77 respectively
Abbreviated MRI[121]	86%	94%	· Sensitivity of AMRI for detection of HCC <2 cm versus HCC ≥2 cm (69% vs. 86%) · Non-contrast AMRI versus contrast-enhanced AMRI (sensitivity 86% and 94% vs. specificity 87% and 94%, respectively)
Six-marker methylated DNA marker (MDM) panel[119]	95%	92%	· Including *HOXA1, EMX1, AK055957, ECE1, PFKP, CLEC11A* normalized by *B3GALT6* level · AUC of 0.96 (95% CI, 0.93–0.99) in a phase 2 trial
Extracellular vesicle (EV) surface protein assay[120]	91% (early-stage HCC)	90% (early-stage HCC)	· AUC of 0.95 (95% CI, 0.90–0.99) in early-stage HCC

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AUC, area under the curve; AUROC, Area Under the Receiver Operating Characteristic curve; CI, confidence interval; DCP, des gamma carboxy prothrombin; FPR, false positive rate; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.

https://doi.org/10.3350/cmh.2024.0824

tients with cirrhosis (NCT06084234).

Liquid biopsy is also emerging as a supplementary approach to imaging for the early detection of HCC, which consists of analysis of circulating tumor DNA, tumor cells, or tumor-derived extracellular vesicles (EV).[117] Methylation profiling of circulating tumor DNA has evolved as a promising surveillance tool for detecting early HCC in at-risk populations, although phase 3 biomarker validation studies are yet to be done.[117,118] A recent phase 2 study on a six-marker methylated DNA marker panel (*HOXA1, EMX1, AK055957, ECE1, PFKP, CLEC11A*) yielded an area under the curve (AUC) of 0.96 with a sensitivity of 95% and specificity of 92%.[119] An algorithm incorporating sex and AFP levels with the methylation biomarkers (HOXA1, TSPYL5, and B3GALT6) was also developed, showing a higher early-stage sensitivity compared to AFP level (≥20 ng/mL) and GALAD (≥−0.63), although specificity was lower.[118] In addition, the HCC EV surface protein assay based on four HCC-associated surface protein markers and two EV markers is also a promising circulating biomarker for early-stage HCC detection and was validated in a phase 2 study.[120] These strategies are promising, although most data are limited to case-control studies, which can overestimate performance, and prospective validation in cohort studies is needed prior to adoption.

An abbreviated MRI has been a suggested alternative imaging modality to improve sensitivity since a complete MRI is not feasible as a surveillance tool due to prolonged scanning time. A pooled estimate of 15 studies demonstrated 86% sensitivity and 94% specificity per patient, comparable in sensitivity and specificity between non-contrast and contrast-enhanced MRI.[121] Abbreviated MRI is undergoing prospective validation in large trials in the US, France, and South Korea (NCT05486572, NCT05095714, NCT06312826).[122] Although these studies show high test performance, issues including radiological capacity, costs, and patient acceptance would need to be considered for implementation.

Follow-up after surveillance

Follow-up of surveillance test results for subsequent procedures or diagnostic testing is recommended based on the LI-RADS (Liver Imaging Reporting and Data System) visualization score, size of the lesion, and AFP levels.[86] Patients with well-visualized sonography (visualization A) with no lesions and normal AFP levels can repeat surveillance in 6 months.

For patients with subcentimeter liver lesions in ultrasound, a short-interval repeat test in 3–4 months is reasonable when the initial ultrasound demonstrated optimal visualization.[123] However, patients with suboptimal ultrasound visualization or increased odds of poor visualization, such as obesity, alcohol-related liver disease, or MASLD cirrhosis, should be considered for further computed tomography (CT) or MRI.[124] For patients with lesions that are more than 1 cm on the ultrasound, AFP levels over 20 ng/mL, or increasing AFP levels, diagnostic contrast-enhanced multiphase MRI or CT should be performed.

CT/MRI LI-RADS is used to further characterize abnormal imaging findings.[125] For LR-1 (definitely benign) and LR-2 (probably benign) lesions, return to ultrasound surveillance at a routine 6-month interval is recommended for LR-1 observations, while follow-up CT or MRI in 6 months or less may be considered for LR-2 observations. For LR-3 (intermediate probability of HCC) lesions, close monitoring with follow-up CT or MRI in 3 to 6 months is warranted because approximately 30% to 40% of LR-3 observations may represent HCC. For LR-4 (probably HCC) lesions, multidisciplinary discussion for tailored workup is recommended with options including a biopsy or repeated imaging in a short interval of around 3 months. LR-5 is diagnostic for HCC, as discussed further in the following section.

DIAGNOSIS OF HCC

HCC, unlike most cancers, can be diagnosed in at-risk patients such as patients with cirrhosis or chronic HBV infection using specific non-invasive imaging criteria, without the need for histologic confirmation.[86] This unique feature is due to the specific pattern of angiogenesis during hepatocarcinogenesis in which HCC is dominantly supplied by the hepatic artery whereas the liver parenchyma is supplied by both the portal vein (75%) and hepatic artery (25%).[126,127] The LI-RADS categorizes liver nodules based on 1) the presence of arterial phase hyperenhancement, 2) the size of the nodule, and 3) the number of additional major features including enhancing “capsule”, non-peripheral “washout”, threshold growth and LR-5, is diagnostic for

HCC.[128] An important caveat of the LI-RADS criteria is that it is only applicable in at-risk populations (i.e., cirrhosis, chronic hepatitis B, history of HCC), and liver biopsy is still required otherwise for histologic confirmation.[128]

Pathological diagnosis is required for indeterminate focal lesions, which have atypical imaging features, and for patients without cirrhosis or HBV infection, in whom the LI-RADS criteria do not apply.[86,87] Routine biopsy could be considered before initiation of systemic therapy, particularly considering emerging data suggesting that up to 10% of patients with larger tumor burden can have other diagnoses (e.g., mixed HCC-CCA, CCA, or neuroendocrine), which would change the choice of systemic therapy.[129] Pathological diagnosis of HCC should be based on the criteria of the WHO classification and International Consensus recommendations using the required histological and immunohistological analyses.[87]

Tissue and/or ctDNA profiling using the next generation sequencing (NGS) method is a novel oncological diagnostic with identified common mutations such as *TERT, TP53, CTNNB1*, and *AXIN1*.[130] With the emergence of various systemic therapies, NGS has the potential to establish a foundation for making decisions regarding personalized therapy. HCC has demonstrated significant intertumoral genomic heterogeneity, with different patterns of HCC evolution and high molecular heterogeneity in multiple regions of the same tumor nodule. Thus, a liquid biopsy might have a role in the comprehensive monitoring of evolution of the molecular landscape of HCC.[131]

TREATMENT

Staging is the first step to determining the treatment plan for HCC but remains challenging as it should incorporate not only tumor burden, but the underlying liver dysfunction, other medical comorbidities, performance status, and ultimately reflecting prognosis. The BCLC staging system is the most widely validated and incorporated into most society guidelines. The BCLC staging system takes into ac-

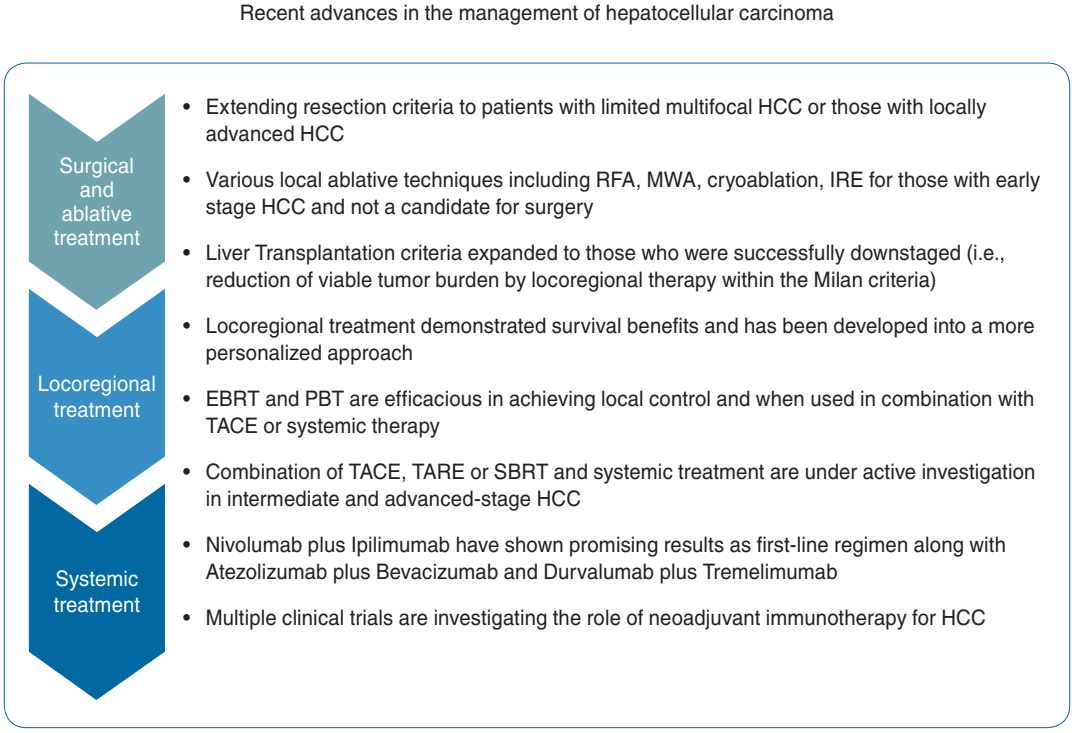

Figure 2. Recent advances in the management of hepatocellular carcinoma. Created in BioRender. Hwang S (2024) https://BioRender.com/u75r972. EBRT, external beam radiation therapy; HCC, hepatocellular carcinoma; IRE, irreversible electroporatio; MWA, microwave ablation; PBT, proton beam therapy; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

https://doi.org/10.3350/cmh.2024.0824

count the tumor burden (including the number and size of nodules, vascular invasion, extrahepatic spread), liver dysfunction, and performance status and is classified into 5 stages; very early stage (0), early stage (A), intermediate stage (B), advanced stage (C), and terminal stage (D).[132] However, there is a recognition of heterogeneity within BCLC stages, which can impact recommended treatment strategies, so alternative staging systems have been proposed.[133,134]

There has been a rapid revolution in HCC treatment over the past decade (Fig. 2). Patients with very early-stage and early-stage tumors are potential candidates for curative treatment, including liver transplantation (LT), local ablation, or surgical resection. Intermediate-stage tumors, i.e., localized to the liver but beyond early stage, are often considered for locoregional therapies such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE) with yttrium-90 (Y90), although systemic therapy is considered for some patients with large tumor burden. The mainstay of treatment for patients with advanced-stage tumors is systemic therapy, although some patients with locally advanced tumors (e.g., branch tumor thrombus) can be treated with surgical treatment or local therapies such as TARE.[132] Patients often transition from one treatment to the other with disease progression or response over time.[135]

A multidisciplinary approach involving the collaboration of healthcare professionals from various fields is recommended for all HCC patients due to the complexity of HCC staging and management, as well as rapidly emerging treatment options. This has been associated with improved overall survival and an increased chance of patients receiving curative treatment.[136] The role of the multidisciplinary team is to confirm the diagnosis and staging of HCC and formulate a treatment plan such as identifying candidates for surgical resection for early-stage HCC, as well as promptly identifying those eligible for liver transplant.[137] Multidisciplinary care is important not only at the initial presentation but also throughout a patient's treatment course.

Surgical resection

Patients with localized HCC without evidence of vascular invasion or extrahepatic metastases are suitable candidates for liver resection. The underlying liver function and presence of portal hypertension (defined as HVPG ≤10 mmHg) play a major role in determining resectability.[138] Although most data are limited to BCLC 0 or A stages, studies on extending resection criteria to select patients with limited multifocal HCC or those with locally advanced HCC have suggested survival benefits compared to TACE or radiofrequency ablation (RFA). It suggests that, for early multinodular HCC patients ineligible for transplant, resection should be prioritized.[139-145] Most of the data for these extended indications are derived from Asian cohorts, with fewer data from Western cohorts in non-HBV populations. Minimally invasive liver resection including laparoscopic and robotic approaches is applied more to reduce morbidity and mortality.[146] Recurrence occurs in more than half of the patients undergoing surgical resection, mostly within 2 years. Nevertheless, surgical resection can achieve long-term survival by detecting and treating recurrent tumor early.[147-149]

Local ablation

Local ablation is highly effective for tumors up to 3 cm in diameter. RFA and microwave ablation (MWA) are commonly used ablation treatments, although other ablative modalities are available with similar outcomes.[150] RFA induces radiofrequency-generated heat to destroy tumoral tissue and its efficacy has been demonstrated in early HCC patients.[151] MWA uses high-frequency electromagnetic energy to induce tissue death with large tumor ablation volumes, faster ablation time, and lower risk of heat-sink effect.[152,153] Although the local recurrence rate and disease-free survival rate were similar between RFA versus MWA, MWA had a lower distant recurrence rate, potentially decreasing the rate of long-term recurrences.[154] Both are a valuable option for patients who are not a candidate for surgery due to tumor size, number, central location, impaired liver function, or comorbidities and are a cost-effective option compared to surgery.[155,156] Depending on the location of the tumor, RFA can be adopted as first-line due to excellent local control of small HCC.[87,157] It has also been proven effective as downstaging and bridging therapy in the pre-transplant setting.[158] However, its efficacy diminishes in patients with large lesions (more than 3 cm) or lesions adjacent to large vessels.[86] Alternative treatment should be considered in patients with HCC adjacent to other critical

structures, including central bile ducts, or if the area is not accessible via a percutaneous method. Similar to surgical resection, the high rate of tumor recurrence and/or distant metastasis remains a challenge.[159] Furthermore, there are alternative ablative modalities such as cryoablation which demonstrated lower local tumor progression and equivalent efficacy and safety compared to RFA in a multicenter RCT,[160] or irreversible electroporation which utilizes short pulses of direct current at high voltage through multiple electrodes and recently demonstrated efficacy in a clinical setting on HCC patients.[161]

Neoadjuvant and adjuvant treatment

Systemic therapies in the adjuvant and neoadjuvant settings for early-stage HCC have been investigated recently. In a phase 3 trial of adjuvant treatment with sorafenib after HCC surgical resection or local ablation, there was no benefit compared to the placebo in recurrence-free survival.[162] The IMbrave 050 study was the first phase 3 study to report positive results. There was a significantly improved recurrence-free survival (HR 0.72, 95% confidence interval [CI] 0.53–0.98) in the adjuvant therapy group (atezolizumab plus bevacizumab) vs. control group of high-risk HCC patients after curative-intent surgical resection or ablation.[163] However, more recently, longer follow-up results suggested a lack of improvement in progression-free survival.[164] Neoadjuvant therapies are also promising in priming the immune system to prevent recurrence and downstaging of locally advanced tumors for surgical resection or liver transplants.[165] HCC develops in a setting of chronic inflammation of the liver in which the microenvironment is altered and immune cells are altered; thus, several synergistic mechanisms for the efficacy of neoadjuvant immunotherapy have been proposed.[165] Neoadjuvant cabozantinib and nivolumab converted locally advanced HCC into resectable disease (80% with margin negative resection, 42% with major pathologic response) in a total of 15 patients.[166] A phase 2 study on perioperative nivolumab and nivolumab plus ipilimumab was safe and tolerable. 33% of the patients achieved major pathological response (MPR) and 5/6 MPR patients achieved complete response.[167] Multiple phase 1–2 clinical trials are ongoing to investigate the role of neoadjuvant immunotherapy for HCC (NCT05908786, NCT03299946, NCT05471674, NCT04224480, NCT03337841, NCT05440864, NCT03682276, NCT03510871, NCT04658147, NCT04123379).

LT

LT is an optimal treatment option for early-stage, unresectable HCC in patients with cirrhosis as it can not only remove intrahepatic tumors but also cure the underlying cirrhosis. About 15% of patients experience HCC recurrence after LT with a mortality rate of 19.8% at 5 years and 35.7% at 10 years in patients receiving deceased donor LT (DDLT). There has been a significant improvement in transplant outcomes over the past few decades.[168,169] The selection of patients for LT has been historically guided by the Milan criteria (one tumor that is less than 5 cm in diameter; up to three tumors, each less than 3 cm in diameter) while there were ongoing efforts on extending the patient population eligible for LT.[170] Additional criteria have also been proposed such as the UCSF criteria where the overall size limitation has expanded (one tumor ≤6.5 cm in diameter or up to three tumors ≤4.5 cm with total tumor diameter ≤8 cm) with no significant difference in 5-year follow-up.[171-173] Successful downstaging, defined as a reduction of viable tumor burden by locoregional therapy within the Milan criteria, demonstrates good post-LT outcomes and is currently adopted in the United Network for Organ Sharing (UNOS) in the U.S.[174,175] Over 80% of the cases had a successful down-staging rate with HCC within the UNOS-DS criteria (a single lesion greater than 5 cm and up to 8 cm; two to three lesions, with at least one lesion less than 3 cm and each 5 cm, with a total tumor diameter of 8 cm; four to five lesions, each less than 3 cm, with a total tumor diameter of 8 cm).[176] The outcome of "all-comers," HCC exceeding UNOS-DS criteria in regard to primary tumor burden, had a slightly lower successful downstaging but acceptable rate (67%), suggesting that it is a realistic goal in selected all-comer patients.[177]

Salvage LT is also a strategy for patients with HCC who have undergone resection and developed tumor recurrence within the LT criteria or liver decompensation.[178,179] It has shown better disease-free survival compared to second resection for recurrent HCC.[180] A major limitation of LT has been organ shortage, and living donor LT (LDLT) has been a viable option, especially in Asia.[181] LDLT recipients showed comparable long-term outcomes compared to

https://doi.org/10.3350/cmh.2024.0824

DDLT recipients. LDLT may provide better survival benefits, especially in regions that had low deceased organ availability.[182]

TACE and TARE

TACE is the standard of care treatment for intermediate-stage HCC with well-defined nodules, preserved portal flow, and selective access.[86,183] It is a method of injecting chemotherapy into tumor-feeding arteries while hindering the arterial blood supply to the tumor, inducing tumor necrosis.[184] Two RCTs confirmed the survival benefit of TACE for unresectable HCC.[185,186] It is often used as a bridging or downstaging therapy for the patient to be a candidate for LT or resection.[184] However, challenges remain as patients may develop TACE-refractory tumors or experience failure to achieve objective response after two or more treatments.[187] Furthermore, transarterial embolization using microspheres alone when compared to TACE demonstrated no difference in RECIST response in a randomized trial in a single tertiary center, challenging the role of chemotherapy.[188]

TARE delivers radioactive microspheres loaded with Y90 leading to tumor destruction with excellent efficacy in solitary HCC.[189] A phase 2 study randomized BCLC stage B or C, Child-Pugh stage A patients with unablatable/unresectable HCC to either Y90 therapy or TACE and was able to demonstrate that the Y90 radioembolization group had a significantly longer median time to progression (TTP) (>26 versus 6.8 months) with better tumor control and increased likelihood to receive transplantation and slightly favorable side effect profile.[190] The superiority of TARE in terms of TTP was insufficient to prolong the overall survival compared to TACE.[191] However, prolonging TTP through TARE can provide higher rates of successful bridging to transplantation, especially as Y90 is an intra-arterial therapy that eliminates the risk of tract seeding. TARE is better tolerated than TACE.[190] The TRACE phase 2 RCT compared Y90 glass TARE with doxorubicin drug-eluting bead TACE and demonstrated superiority in tumor control and overall survival.[192] In addition, a phase 2 trial (DOSISPHERE-01) reported a personalized dosimetry approach delivering at least 205 Gy to the index lesion improved overall survival, especially in patients downstaged for resection compared to the prior standardized approach, highlighting the importance of using personalized dosimetry.[193]

External beam radiation treatment

Stereotactic body radiation therapy (SBRT) is an emerging treatment option across early, intermediate and advanced stages of HCC.[194] It is a modality that delivers high doses of conformal radiation to the tumors in 1–5 fractions, enabling a precise steep dose gradient without involving the surrounding structures including the liver.[194-196] It is a promising alternative to RFA or TACE in terms of local control but also demonstrated superior outcomes when combined with TACE plus RT compared to TACE alone.[197,198] Patients with advanced HCC and macroscopic vascular invasion may also benefit from first-line treatment with TACE plus RT vs sorafenib, although superiority of this combination approach to systemic treatment needs to be revisited given the improved efficacy of systemic treatment with the introduction of ICI.[199]

Proton beam therapy is also an emerging option that is non-invasive and used in locations that are unsuitable for other local treatments such as RFA or surgery.[200] In a phase 3 clinical trial on recurrent/residual HCC (size <3 cm, number ≤2), patients were randomized to proton beam and RFA. Proton beam therapy was non-inferior to RFA with 2-year local progression-free survival being 92.8% vs. 83.2%.[201] Of note, crossover was permitted and PBT demonstrated greater feasibility than RFA, with a notably lower crossover rate (8.3 versus 26.4%).[201] Overall, external beam radiation treatment is a viable option for early-to-intermediate stage HCC in achieving local control and is promising in combination therapies with TACE in intermediate-stage, and combination with systemic therapy in advanced HCC, especially with vascular invasion.[199,200]

Systemic treatment

Systemic treatment is indicated for unresectable advanced-stage HCC, intermediate-stage HCC with extensive, infiltrative liver involvement, and those who had disease progression despite locoregional therapy or are poor candidates for locoregional treatment.[86] Tyrosine kinase inhibitors (TKI) and ICI with or without anti-vascular endothelial growth factor (VEGF) inhibitors have become the mainstay of systemic treatment for HCC (Table 3).[163,202-213] When

Table 3. Summary of the efficacy of systemic treatment with proven benefit in phase 3 RCTs

First-line treatment				
Monotherapy (TKIs/ICIs)				
	Study population	**Comparator**	**Median overall survival**	**Hazard ratio (95% CI)**
Systemic treatment (Trial)				
Sorafenib (SHARP)[206]	Advanced HCC patients without prior systemic therapy, ECOG PS 0-2 and Child-Pugh class A	Sorafenib 400 mg twice daily versus placebo	10.7 vs. 7.9 mo	0.69 (0.55–0.87)
Lenvatinib (REFLECT)[207]	Unresectable HCC, BCLC stage B or C, Child-Pugh class A, ECOG PS 0-1	Lenvatinib 12 mg/day (for body weight ≥60 kg) or 8 mg/day (for body weights <60 kg) versus sorafenib 400 mg twice daily (non-inferiority trial)	13.6 vs. 12.3 mo	0.92 (0.79–1.06)
Tislelizumab (RATIONALE-301)[212]	HCC with disease progression following (or patient not amenable to) locoregional therapy BCLC stage B or C, Child-Pugh class A, ECOG 0-1	Tislelizumab, 200 mg intravenously every 3 wk, or sorafenib tosylate, 400 mg orally twice daily (non-inferiority trial)	15.9 vs. 14.1 mo	0.85 (0.71–1.02)
Combination therapy				
Nivolumab+Ipilimumab (CheckMate-9DW)[205]	Previously untreated HCC not eligible for curative Tx, Child-Pugh score 5-6, ECOG PS 0-1	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg followed by nivolumab 480 mg every 4 wk versus lenvatinib 8 or 12 mg daily or sorafenib 400 mg twice daily	23.7 vs. 20.6 mo	0.79 (0.65–0.96)
Atezolizumab+bevacizumab (IMBrave150)[202]	Unresectable HCC, Child-Pugh class A, ECOG 0-1	Atezolizumab 1,200 mg plus bevacizumab 15 mg/kg every 3 wk versus sorafenib 400 mg twice daily	NE vs. 13.2 mo	0.58 (0.42–0.79)
Tremelimumab+durvalumab (HIMALAYA)[203]	HCC patients ineligible for locoregional therapy, BCLC stage B or C, Child-Pugh class A, ECOG 0-1	STRIDE (tremelimumab 300 mg plus durvalumab 1,500 mg) versus durvalumab 1,500 mg versus sorafenib 400 mg twice daily	16.43 vs. 16.56 vs. 13.77 mo	0.78 (0.65–0.93) (STRIDE) 0.86 (0.73–1.03) (Durvalumab)
Camrelizumab+rivoceranib (CARES-310)[213]	Advanced HCC in patients not amenable to or had progressed after surgical or locoregional therapy, BCLC stage B or C, Child-Pugh class A, ECOG 0-1	Camrelizumab 200 mg IV every 2 wk plus rivoceranib 250 mg orally once daily versus sorafenib 400 mg twice daily	22.1 vs. 15.2 mo	0.62 (0.49–0.80)

https://doi.org/10.3350/cmh.2024.0824

https://doi.org/10.3350/cmh.2024.0824

Table 3. Continued

First-line treatment				
Monotherapy (TKIs/ICIs)				
	Study population	**Comparator**	**Median overall survival**	**Hazard ratio (95% CI)**
Second or subsequent line treatment				
Monotherapy (TKIs/ICIs)				
Regorafenib (RESOURCE)[208]	HCC patients who tolerated but progressed on sorafenib, Child-Pugh class A	Regorafenib 160 mg daily versus placebo	10.6 vs. 7.8 mo	0.63 (0.50–0.79)
Cabozantinib (CELESTIAL)[209]	HCC patients who received previous treatment with sorafenib and had had disease progression after at least one systemic treatment (received up to 2), Child-Pugh class A, ECOG PS 0-1	Cabozantinib 60 mg daily versus placebo	10.2 vs. 8.0 mo	0.76 (0.63–0.92)
Ramucirumab (REACH-2)[210]	BCLC stage B or C, Child-Pugh class A, ECOG PS 0-1, AFP ≥400 ng/mL	Ramucirumab 8 mg/kg versus placebo	8.5 vs. 7.3 mo	0.710 (0.531–0.949)
Pembrolizumab (CheckMate 240)[211]	HCC patients who progressed from or intolerable to sorafenib, BCLC stage B or C, Child-Pugh class A, ECOG 0-1	Pembrolizumab 200 mg every 3 wk versus placebo	13.9 vs. 10.6 mo	0.77 (0.62–0.96)
Combination therapy				
Nivolumab+Ipilimumab (CheckMate 040)[204]	Advanced HCC patients previously treated with sorafenib, Child-Pugh class A, ECOG PS 0-1	Nivolumab 1 mg/kg plus ipilimumab 3 mg/kg followed by nivolumab 240 mg every 2 wk (arm A); nivolumab 3 mg/kg plus ipilimumab 1 mg/kg followed by nivolumab 240 mg every 2 wk (arm B); or nivolumab 3 mg/kg every 2 wk plus ipilimumab 1 mg/kg every 6 wk (arm C)	22.8 mo (arm A) vs. 12.5 mo (arm B) vs. 12.7 mo (arm C)	-
Adjuvant therapy				
Atezolizumab+bevacizumab (IMbrave050)[163]	High-risk surgically resected or ablated HCC	Atezolizumab 1,200 mg plus bevacizumab 15 mg/kg every 3 wk versus active surveillance (adjuvant therapy)	-	0.72 (0.53–0.98) for recurrence free survival*

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ICI, immune checkpoint inhibitor; HCC, hepatocellular carcinoma; NE, not evaluated; RCT, randomized controlled trial; TKI, tyrosine kinase inhibitors.

*Needs to be interpreted with caution as updated efficacy and safety data does not demonstrate consistent results with longer follow-up.[162]

deciding on the appropriate systemic therapy, several factors need to be considered. For example, history of autoimmune disease or prior adverse events needs to be considered when starting an ICI, whereas a history of cardiac comorbidities or risk of bleeding/thrombosis should be accounted for before initiation of an anti-angiogenic treatment.[214] Screening for esophageal varices is recommended before initiating therapy with bevacizumab due to the potential adverse effects of gastrointestinal bleeding associated with the treatment.[215]

First-line treatment

Atezolizumab (anti-PDL1) plus bevacizumab, an antiangiogenic agent, has become the standard of care and the first-line regimen for patients with advanced HCC after the IMbrave 150 clinical trial in 2020.[202,215] This has also been validated by several studies regarding its efficacy and safety profile/tolerance in Child-Pugh class B patients, although the presence of main portal vein tumor thrombus and a higher albumin-bilirubin (ALBI) grade was associated with a poorer prognosis.[216,217] The combination treatment of durvalumab and tremelimumab is also currently approved as the first-line regimen for patients with advanced HCC.[214] A phase 3 trial demonstrated that STRIDE (Single Tremelimumab Regular Interval Durvalumab) significantly improved overall survival (HR 0.78, 95% CI 0.65–0.93) compared to sorafenib, and durvalumab monotherapy was non-inferior to sorafenib for patients with unresectable HCC.[203] The main factor to consider in selecting first-line combination regimens between the two is whether the patient can tolerate an anti-VEGF inhibitor.[218] While nivolumab plus ipilimumab was tested before as second-line (CheckMate-040), a recent phase 3 study (CheckMate-9DW) on first-line nivolumab plus ipilimumab compared to sorafenib or lenvatinib reported improved median overall survival (23.7 versus 20.6 months, HR 0.79, 95% CI 0.65–0.96) suggesting that this combination ICI therapy will likely be approved as a first-line regimen for unresectable HCC soon.[204,205]

Sorafenib is the first TKI that showed improved survival and TTP in untreated advanced HCC with Child-Pugh class A.[206] It is also the treatment of choice for advanced HCC recurrence after LT, although drug-to-drug interactions with immunosuppressants should be closely monitored.[219] Lenvatinib, another TKI, has subsequently demonstrated non-inferiority (vs. sorafenib) in overall survival in the REFLECT trial.[207]

Subsequent line treatment

Regorafenib was shown to improve overall survival in BCLC stage B or C HCC patients not eligible for local treatment who previously progressed on sorafenib in the RESOURCE study[208] and cabozantinib demonstrated improved survival in HCC not amenable to curative treatment with up to 2 lines of prior treatment including sorafenib.[209] Ramucirumab, a monoclonal antibody against VEGF2, was studied in BCLC stage B or C HCC patients previously treated with sorafenib and with an AFP above 400 ng/mL and showed improved median overall survival compared to placebo.[210] Pembrolizumab showed efficacy in a phase 3 trial in advanced HCC, previously treated with sorafenib compared to placebo.[211] These treatments were U.S. FDA-approved as subsequent line treatments for advanced HCC.

Combination of systemic and locoregional treatment

Combining systemic treatment with other modalities such as ablation, TACE, TARE or SBRT is expected to improve outcomes and is under active investigation in intermediate and advanced-stage HCC. For example, local ablation in combination with tremelimumab showed additional increased immunogenicity effects, leading to increased intratumoral CD8+ cells and reduction in HCV viral load.[220] The EMERALD-1 is a phase 3 trial that demonstrated improvement in PFS with the combination of ICI plus VEGF inhibitor and TACE compared to only TACE in patients with embolization-eligible unresectable HCC, Child-Pugh A to B7 liver function, ECOG 0–1, and no evidence of extrahepatic disease, though there needs to be caution as further studies need to explore overall survival and the safety profile.[221] There was also a recent study comparing the addition of a locoregional therapy to systemic therapy in advanced HCC. TACE-ICI-VEGF treatment, versus ICI-VEGF, exhibited improved median OS (22.6 months versus 15.9 months) and higher ORR (47.3% versus 29.7%).[222]

An important caveat is that these phase 3 clinical trials were performed in select populations with preserved liver

https://doi.org/10.3350/cmh.2024.0824

function (e.g., Child-Pugh class A liver disease) and good performance (ECOG PS 0 or 1) status, limiting generalizability of the efficacy and safety of treatment in patients with more comorbid conditions.[223] ICI treatment should be considered and further studied in patients with advanced liver dysfunction given its tolerability; a meta-analysis found that Child-Pugh class B HCC patients had a comparable safety profile from ICI treatment and response rate compared to Child-Pugh class A patients but poorer prognosis in overall survival due to higher competing risk of death from liver failure.[224] Furthermore, although various combination therapies are being studied, the identification of biomarkers to predict the response to systemic therapies such as ICI or TKI is limited with few relevant studies to date.[225] Lastly, the financial burden of systemic treatment is substantial and should be better understood and taken into consideration in selecting a treatment strategy for HCC.[226]

BEST SUPPORTIVE CARE (BSC)

Palliative care can be provided alongside active treatment, but it can also be chosen as the only treatment option when disease-modifying therapies are unavailable, referred to as BSC. Symptom management especially in the terminal stage includes managing complications of liver failure such as ascites and encephalopathy, pain or dyspnea from metastatic disease, and fatigue or anorexia from extrahepatic symptoms.[227] Furthermore, the palliative care team can partake in advance care planning discussions before treatment, and provide support around treatment decisions as well as end-of-life preferences or hospice.[228]

CONCLUSION

The landscape of HCC care continuum has transformed dynamically in recent years. The increasing burden of MASLD has brought a challenge in the selection of the population that is eligible for HCC surveillance which subsequently affects the surveillance implementation, policy and appropriate modality for surveillance. Diagnostics are shifting towards precision medicine along with the various treatment options that have emerged. With the advance of locoregional therapy and downstaging HCC, the candidates for LT have been broadened with promising outcomes. Systemic treatment with ICIs and TKIs has become the backbone of advanced HCC with its applications broadening in the neoadjuvant and adjuvant settings. Studies combining different modalities such as locoregional therapy and systemic therapy in intermediate and advanced HCC are also being actively performed with promising results.

Authors' contributions

Concept and design: SYH, PD, JDY. Administrative Support: JDY. Writing, original draft: SYH, PD. Writing, review, and editing: VA, NM, NDP, GKA, AGS, JDY. Final Approval and Agreement: All Authors.

Acknowledgements

Dr. Singal's research is supported by NCI R01 MD012565 and R01 CA256977. Dr. Yang's research is supported by NCI K08CA259534.

Conflicts of Interest

Ju Dong Yang provides a consulting service for AstraZeneca, Eisai, Exact Sciences, Exelixis, Fujifilm Medical Sciences. Neehar Parikh has served as a consultant or advisor for Genentech, Fujifilm Medical, Eisai, Exelixis, Merck, Exact Sciences, Freenome, and Gilead. Ghassan K. Abou-Alfa reports research support from Agenus, Arcus, Astra Zeneca, BioNtech, BMS, Elicio, Genentech/Roche, Helsinn, Parker Institute, Pertzye, Puma, QED, Servier, Yiviva and consulting support from Abbvie, Alligator Astra Zeneca, Autem, Berry Genomics, BioNtech, Boehringer Ingelheim, BMS, Eisai, Exelixis, Genentech/Roche, Incyte, Ipsen, J-Pharma, Merck, Merus, Neogene, Novartis, Servier, Tango, Tempus, Vector, Yiviva.

Amit Singal has served as a consultant or on advisory boards for Genentech, AztraZeneca, Eisai, Exelixis, Bayer, Merck, Elevar, Boston Scientific, Sirtex, Histosonics, FujiFilm Medical Sciences, Exact Sciences, Roche, Glycotest, Abbott, and GRAIL.

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