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A concise review of updated global guidelines for the management of hepatocellular carcinoma: 2017-2024

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Many guidelines for hepatocellular carcinoma (HCC) have been published and are regularly updated worldwide. HCC management involves a broad range of treatment options and requires multidisciplinary care, resulting in significant heterogeneity in management practices across international communities. To support standardized care for HCC, we systematically appraised 13 globally recognized guidelines and expert consensus statements, including five from Asia, four from Europe, and four from the United States. These guidelines share similarities but reveal notable discrepancies in surveillance strategies, treatment allocation, and other recommendations. Geographic differences in tumor biology (e.g., prevalence of viral hepatitis, alcohol-related liver disease, or metabolic dysfunction-associated steatotic liver disease) and disparities in available medical resources (e.g., organ availability, healthcare infrastructure, and treatment accessibility) complicate the creation of universally applicable guidelines. Previously, significant gaps existed between Asian and Western guidelines, particularly regarding treatment strategies. However, these differences have diminished over the years. Presently, variations are often more attributable to publication dates than to regional differences. Nonetheless, Asia-Pacific experts continue to diverge from the Barcelona Clinic Liver Cancer system, particularly with respect to surgical resection and locoregional therapies, which are viewed as overly conservative in Western guidelines. Advancements in systemic therapies have prompted ongoing updates to these guidelines. Given that each set of guidelines reflects distinct regional characteristics, strengths, and limitations, fostering collaboration and mutual complementarity is essential for addressing discrepancies and advancing global HCC care. **(J Liver Cancer 2025;25:19-30)**

Keywords: Carcinoma, hepatocellular; Transplantation; Therapeutic chemoembolization; Chemotherapy; BCLC

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer-associated deaths worldwide, with more than 750,000 deaths reported annually.[1] However, the overall prognosis remains poor, with a median survival of 6-24 months,[2,3] despite significant advancements in treatment over the past decade.[4,5] Numerous international hepatology societies have evaluated HCC management and treatment strategies and released corresponding guidelines.[6-12]

Clinical practice guidelines are defined as statements that include recommendations intended to optimize patient care, informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.[13] Proper implementation of these guidelines can help achieve key objectives, including supporting medical practitioners in making informed decisions, enhancing healthcare quality and patient outcomes, and providing guidance to local or national authorities regarding resource allocation.

Many HCC guidelines have been published globally, demon-

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Table 1. Current guidelines for the management of HCC across different regions

Region	Organization	Guideline	Publishing year	Distinctive feature
Asia	KLCA-NCC	2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma	2023	Comprehensive overview from prevention to palliative treatment Utilization of resection and combination of locoregional treatments in advanced-stage HCC
	JSH	Management of hepatocellular carcinoma in Japan: JSH consensus statements and recommendations 2021 update	2021	Defines the extremely high-risk group and proposes a surveillance strategy
		Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2021 version (5th JSH-HCC guidelines)	2023	Presents concise algorithms for surveillance, diagnosis, and treatment
	TLCA	Management consensus guidelines for hepatocellular carcinoma: 2023 update on surveillance, diagnosis, systemic treatment and posttreatment monitoring by the TLCA and the Gastroenterological Society of Taiwan	2024	Utilization of biomarkers other than AFP in the surveillance setting Suggests systemic therapy for patients with TACE refractoriness or unsuitability
	APASL	Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update	2017	Recently updated guidelines for systemic therapy Includes etiologies from across the Asia region
		APASL clinical practice guidelines on systemic therapy for hepatocellular carcinoma-2024	2024	Diagnosis and surveillance explained according to imaging modalities
	APPLE	A changing paradigm for the treatment of intermediate-stage hepatocellular carcinoma: APPLE consensus statements	2020	Focus on the treatment of intermediate-stage HCC and TACE-unsuitable cases
Europe	BSG	British Society of Gastroenterology guidelines for the management of hepatocellular carcinoma in adults	2024	Adopts risk stratification scores for surveillance of CHB patients Includes the most recent first-line systemic therapies
	BCLC	BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update	2022	Focus on staging and treatment allocation Presents clinical decision-making as a key process
	EASL	EASL clinical practice guidelines: management of hepatocellular carcinoma	2018	Comprehensive overview from prevention to palliative treatment
	ESMO	Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up	2018	Mostly based on the modified BCLC staging system
		Updated treatment recommendations for hepatocellular carcinoma from the ESMO clinical practice guidelines	2021	Proposes the concept of treatment stage migration
USA	AASLD	AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma	2023	Presents algorithms for each treatment according to staging Utilization of downstaging criteria for LT Broad application of treatments for early-stage HCC
	NCCN	NCCN clinical practice guidelines in oncology (NCCN guidelines®) hepatocellular carcinoma (version 4, 2024)	2024	Does not present the quality of evidence or strength of recommendation Does not follow a specific staging system
	ASCO	Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline update	2024	Focus on systemic therapy
	AGA	AGA clinical practice guideline on systemic therapy for hepatocellular carcinoma	2022	Focus on systemic therapy

HCC, hepatocellular carcinoma; KLCA-NCC, Korean Liver Cancer Association-National Cancer Center of Korea; JSH, Japan Society of Hepatology; TLCA, Taiwan Liver Cancer Association; AFP, α-Fetoprotein; TACE, transarterial chemoembolization; APASL, Asian Pacific Association for the Study of the Liver; APPLE, Asia-Pacific Primary Liver Cancer Expert; BSG, British Society of Gastroenterology; CHB, chronic hepatitis B; BCLC, Barcelona Clinic Liver Cancer; EASL, European Association for the Study of the Liver; ESMO, European Society for Medical Oncology; AASLD, American Association for the Study of Liver Disease; LT, liver transplantation; NCCN, National Comprehensive Cancer Network; ASCO, American Society of Clinical Oncology; AGA, American Gastroenterological Association.

strating overall consistency while being tailored to regional and epidemiological characteristics. In this study, we performed a systematic review of guidelines and expert consensus statements for HCC that were published or updated between 2017 and 2024, building on a review article published in 2016.[14] References meeting the following criteria were included: 1) credibility, determined by the extent to which the guidelines were widely cited in subsequent publications or guidelines on HCC management after their original publication; and 2) influence, reflected in the guidelines being supported by governmental, academic, or medical organizations and their ability to gain national recognition for application and standardized HCC management.

EVALUATION OF CURRENT GUIDELINES AND EXPERT CONSENSUS STATEMENTS FOR HCC

After screening, as shown in Table 1, we selected 13 current guidelines for HCC from around the world, comprising five guidelines from Asia (the Korean Liver Cancer Association [KLCA] and the National Cancer Center of Korea [NCC],[9] the Japan Society of Hepatology [JSH],[15,16] the Taiwan Liver Cancer Association [TLCA], and the Gastroenterological Society of Taiwan [GEST],[17] the Asian Pacific Association for the Study of the Liver [APASL],[6,18] and the Asia-Pacific Primary Liver Cancer Expert [APPLE][19]), four from Europe (the British Society of Gastroenterology [BSG],[20] the European Association for the Study of the Liver [EASL],[7] the European Society for Medical Oncology [ESMO],[8] and the Barcelona Clinic Liver Cancer [BCLC][21]), and four from the United States (the American Association for the Study of Liver Disease [AASLD],[11] the National Comprehensive Cancer Network [NCCN],[12] the American Gastroenterological Association [AGA],[10] and the American Society of Clinical Oncology [ASCO][22]).

Some guidelines focus exclusively on recently updated systemic therapies or are presented as expert consensus statements.[10,18,19,22] This study comparatively evaluated 13 current guidelines to systematically appraise HCC management recommendations.

SURVEILLANCE STRATEGY

Target population

Surveillance refers to the periodic use of a sensitive diagnostic test to detect early disease in a specific high-risk population.[23,24] Most HCC management guidelines consider patients with chronic hepatitis B (CHB) virus infection, hepatitis C virus infection, or cirrhosis as high-risk populations (Table 2). The EASL suggests that surveillance is cost-effective for populations with a predicted HCC incidence of ≥1.5% per year among patients with cirrhosis. However, the AASLD recommends surveillance for at-risk populations with cirrhosis of any etiology if their predicted HCC incidence is ≥1.0% per year, which is lower than the traditional threshold.[25] For individuals with non-cirrhotic CHB, a predicted HCC incidence of ≥0.2% per year is considered sufficient risk to justify surveillance. Notably, both guidelines integrate risk prediction models, such as PAGE-B, to estimate HCC risk in patients with CHB.[26] In contrast, most patients with non-cirrhotic nonalcoholic fatty liver disease or metabolic dysfunction-associated steatotic liver disease are estimated to have an HCC incidence of <0.2% per year.[27] Consequently, risk stratification is essential to determine whether these individuals should be included in surveillance programs.

Tests

Ultrasonography (US) has long been the cornerstone for HCC surveillance,[28,29] with recent meta-analyses reporting a sensitivity of 84% for detecting HCC at all stages and 47% for detecting it at an early stage, along with a specificity of 94-96% when used alone.[30,31] Serum α-fetoprotein (AFP), a traditional tumor marker for HCC diagnosis and recurrence monitoring,[32,33] has a sensitivity of 60-65% and a specificity of 80-84% when using a cut-off point of 20 ng/mL.[31] Combining US with AFP enhances both sensitivity and specificity, providing additional diagnostic value.[34] However, because AFP levels can be elevated in various clinical conditions,[35-37] whether to incorporate AFP into surveillance programs varies across guidelines. The EASL and ESMO advocate for US-only surveillance, whereas more recent guidelines, including those from the BSG, recommend a combination of US and AFP for surveillance.

Computed tomography (CT)- and magnetic resonance imaging (MRI)-based surveillance are generally not recommended. However, the KLCA-NCC guidelines suggest that dynamic contrast-enhanced CT or MRI can be considered an alternative when liver US cannot be performed adequately. Similarly, the JSH and TLCA optionally recommend dynamic CT or MRI for patients who are at an extremely high risk of developing HCC.

Abbreviated MRI (aMRI) protocols have been introduced in

Table 2. Summary of regular surveillance practices across different regions

Region	Guideline	Surveillance				Staging
		Target population		Test	Interval (months)	
Asia	KLCA-NCC	CHB *or* CHC *or* cirrhosis		US *plus* AFP CT or MRI *(inadequate US)*	6	mUICC staging system is primary, with BCLC and AJCC/UICC staging systems as complementary
	JSH	High-risk	CHB *or* CHC *or* non-viral cirrhosis	US *plus* AFP *or* AFP-L3% *or* PIVKA-II	6	Staging is not elaborated in detail
		Extremely high-risk	Cirrhosis with CHB *or* Cirrhosis with CHC	US *plus* AFP *or* AFP-L3% *or* PIVKA-II	3-4	Treatment algorithm based on liver function, extrahepatic metastasis, vascular invasion, tumor number, and tumor size is presented
				CT *or* MRI *(optional)*	6-12	
	TLCA	High-risk	CHB *or* CHC *or* cirrhosis	US *plus* AFP *and/or* PIVKA-II	6	Staging is not elaborated in detail
		Extremely high-risk	Cirrhosis with CHB *or* Cirrhosis with CHC	CT *or* MRI *(optional)*	6-12	Treatment algorithm based on JSH and HKLC, considering extrahepatic metastasis, liver function, vascular invasion, tumor number, and tumor size, is presented
		Inadequate US in high-risk group				
	APASL	Cirrhosis *or* CHB with Asian females >50 years *or* Asian males >40 years *or* Africans >20 years *or* family history of HCC		US *plus* AFP	6	Staging is not elaborated in detail Treatment algorithm based on JSH and HKLC, incorporating extrahepatic metastasis, liver function, resectability, vascular invasion, tumor number, and tumor size, is presented
	APPLE	-		-	-	-
Europe	BSG	Cirrhosis *or* CHB with Asian females >50 years *or* Asian males >40 years *or* Africans >20 years *or* family history of HCC *or* PAGE-B >10		US *plus* AFP	6	BCLC staging system
	EASL	Cirrhosis with Child-Pugh A and B *or* Child-Pugh C transplant candidate *or* CHB with PAGE-B ≥10 *or* non-cirrhotic F3		US	6	BCLC staging system
	ESMO	Cirrhosis with preserved liver function and manageable comorbidities *or* CHB with DNA >10,000 copies/mL *or* CHC with F3		US±AFP	6	BCLC staging system
	BCLC	-		-	-	-
USA	AASLD	Cirrhosis with Child-Pugh A and B *or* Child-Pugh C transplant candidate *or* CHB with females from endemic country >50 years *or* males endemic country >40 years *or* from Africa at earlier age *or* family history of HCC *or* PAGE-B ≥10		US *plus* AFP	6	BCLC staging system
	NCCN	Cirrhosis with Child-Pugh A and B *or* Child-Pugh C transplant candidate *or* CHB		US *plus* AFP	6	No specific staging system is recommended AJCC and BCLC staging systems are introduced
	ASCO	-		-	-	-
	AGA	-		-	-	-

KLCA-NCC, Korean Liver Cancer Association-National Cancer Center of Korea; CHB, chronic hepatitis B; CHC, chronic hepatitis C; US, ultrasonography; AFP, α-fetoprotein; CT, computed tomography; MRI, magnetic resonance imaging; mUICC, modified International Union for Cancer Control; BCLC, Barcelona Clinic Liver Cancer; AJCC, American Joint Committee on Cancer; JSH, Japan Society of Hepatology; AFP-L3%, lens culinaris lectin-binding subfraction of AFP; PIVKA-II, protein induced by vitamin K absence/antagonist-II; TLCA, Taiwan Liver Cancer Association; HKLC, Hong Kong Liver Cancer; APASL, Asian Pacific Association for the Study of the Liver; HCC, hepatocellular carcinoma; APPLE, Asia-Pacific Primary Liver Cancer Expert; BSG, British Society of Gastroenterology; PAGE-B, patient's age, gender, and platelets; EASL, European Association for the Study of the Liver; ESMO, European Society for Medical Oncology; AASLD, American Association for the Study of Liver Disease; NCCN, National Comprehensive Cancer Network; ASCO, American Society of Clinical Oncology; AGA, American Gastroenterological Association.

several recent guidelines. The aMRI uses a limited set of sequences from a full diagnostic protocol, significantly reducing examination time while maintaining promising sensitivity (80-90%) and specificity (91-98%). This approach has the potential to enhance cost-effectiveness and patient acceptance.[38,39]

Several promising biomarkers aside from AFP are currently being evaluated for HCC surveillance, although most require further validation. Two notable blood-based biomarkers are des-gamma carboxyprothrombin (DCP), also known as protein induced by vitamin K absence/antagonist-II (PIVKA-II), and the lens culinaris lectin-binding sub-fraction of AFP (AFP-L3%). These biomarkers are each produced at high levels by a specific subset of HCC. However, AFP, AFP-L3%, and DCP each exhibit insufficient sensitivity when used individually. To address these limitations, the TLCA has recommended complementing AFP with PIVKA-II for surveillance, and the JSH has not restricted the use of tumor markers combined with US to AFP alone. In addition, liquid biopsy approaches, including circulating tumor DNA, tumor cells, and extracellular vesicles, have recently been extensively studied as promising methods to overcome the limitations of current surveillance and diagnostic tools.[40]

Interval

The ideal interval for HCC surveillance should be determined from a cost-effectiveness perspective. Most guidelines recommend semiannual intervals, supported by the reported tumor doubling time of HCC, which ranges from 4 to 7 months, providing a rationale for this recommendation.[41,42] Further analyses have shown that semiannual surveillance is associated with detection of tumors at earlier stages and improved survival compared to annual surveillance.[43] However, a multicenter randomized controlled trial indicated that quarterly surveillance did not enhance the detection of small HCCs or improve survival outcomes, compared to semiannual surveillance.[44] Nevertheless, some guidelines recommend shorter surveillance intervals for patients at extremely high risk.[45,46]

Recall policies

Recall policies are procedures established to address abnormal screening test results and are closely linked to the diagnostic process. Significant differences in recall policies exist among international guidelines, primarily concerning the management of lesions <1 cm. The EASL recommends follow-up at intervals of less than 4 months, considering the high proportion of non-malignant lesions in patients without cirrhosis and the excellent outcomes achievable for lesions up to 2 cm, where a complete response to therapy is almost always possible.[47,48] Similarly, the AASLD recommends follow-up every 3-6 month. For small HCC cases with elevated (≥20 ng/mL) or rising AFP levels, diagnostic multiphasic CT or MRI is recommended. The AASLD also suggests shorter follow-up intervals for patients with suboptimal US visualization.[49,50] The KLCA-NCC recommends follow-up surveillance within a 6-month interval, while the TLCA recommends repeating US, AFP, and/or PIVKA-II every 3-6 month. The JSH offers more specific approaches based on imaging characteristics. For lesions <1 cm in size with arterial phase hyperenhancement (APHE) but no portal or equilibrium phase washout, follow-up US every 3 months is recommended. Similarly, for lesions <1.5 cm without APHE, US follow-up every 3 month is advised.

DIAGNOSIS

Most guidelines recommend that the diagnosis of HCC should be established using non-invasive imaging criteria and/or pathology. However, the EASL and BSG specifically recommend confirming the diagnosis of HCC in patients without cirrhosis by pathology. In contrast, the APASL allows for the diagnosis of typical HCC based solely on imaging, regardless of tumor size, and provides a typical vascular pattern (i.e., arterial enhancement with portal venous washout).

Non-invasive diagnosis

Most current guidelines recommend multiphasic CT, multiphasic MRI with extracellular contrast agents, or multiphasic MRI with hepatocyte-specific contrast agents as the primary diagnostic modality for HCC.[51] Previously observed differences in diagnostic preferences, often due to regional variations in HCC prevalence and liver transplantation allocation policies, have significantly narrowed. However, some guidelines highlight the importance of caution regarding the pseudo-washout effect that can occur when using MRI with hepatocyte-specific contrast agents.[52]

The Liver Imaging Reporting and Data System is widely recommended for HCC diagnosis in at-risk patients with cirrhosis or CHB. A definitive imaging diagnosis of HCC can be made for nodules ≥1 cm identified through surveillance in high-risk patients if they exhibit the following radiological hallmarks:

APHE with washout appearance in the portal venous or delayed phases on multiphasic CT or MRI with extracellular contrast agents, or APHE with washout appearance in the portal venous, delayed, or hepatobiliary phases on multiphasic MRI with hepatocyte-specific contrast agents. These criteria should be applied only to lesions that do not demonstrate marked T2 hyperintensity or a targetoid appearance on diffusion-weighted or contrast-enhanced imaging. For nodules ≥1 cm that do not fulfill the noninvasive diagnostic criteria, a diagnosis of probable HCC can be made by considering ancillary imaging features such as the presence of an enhancing capsule, nonperipheral washout, or threshold growth.[53]

Few guidelines recommend the use of Kupffer phase contrast-enhanced US (CEUS) for the diagnosis of HCC. The APASL and TLCA endorse CEUS as equivalent to multiphase CT or MRI for diagnostic purposes, whereas the EASL and AASLD recommend CEUS as a second-line modality in cases where CT or MRI results are inconclusive, unavailable, or contraindicated, particularly when a tumor biopsy cannot be performed. The AFP level, previously recommended as a diagnostic criterion for HCC at a threshold of 400 ng/mL, is no longer recommended because of its insufficient diagnostic accuracy. Meanwhile, several circulating tumor DNA (ctDNA)-based tests have been approved by the United States Food and Drug Administration (FDA) in oncology, and alterations in ctDNA and ctDNA methylation profiles have shown promise in case-control studies for the early detection and diagnosis of HCC.[40,54] However, these findings require validation in phase III-IV biomarker cohort studies.

Pathological diagnosis

According to all the guidelines, the pathological diagnosis of HCC should adhere to the international consensus recommendations and incorporate the necessary histological and immunohistological analyses. Pathological diagnosis is consistently recommended when imaging does not reveal the characteristic features of HCC. In cases of probable HCC, the KLCA-NCC guidelines recommend repeated imaging or biopsies for pathological confirmation. The AASLD further suggests that biopsy should be included in the diagnostic process, even in cases where imaging strongly indicates definite HCC. Similarly, European guidelines emphasize that HCC diagnosis in patients without cirrhosis should be confirmed through pathology because of the lower specificity of imaging hallmarks in this population, where alternative diagnoses are more frequent.

Staging

Staging systems for clinical decision-making in HCC should account for tumor burden, liver function, and performance status (Table 2). The BCLC staging system is the most widely validated and utilized framework for guiding treatment allocation, as endorsed by many guidelines, including those of the AASLD and EASL. The 2022 revised version of the BCLC staging system emphasizes on treatment stage migration through clinical decision-making, highlighting its adaptability in clinical practice. In contrast, the KLCA-NCC primarily uses the modified International Union for Cancer Control (UICC) staging system, while incorporating the BCLC and American Joint Committee on Cancer (AJCC)/UICC TNM staging systems as complementary tools. Other Asian guidelines do not primarily adopt the BCLC staging system; however, some use it as a reference for treatment planning. The NCCN, on the other hand, does not follow a specific staging system. Instead, it classifies HCC as operable, unresectable, or inoperable based on factors such as performance status and comorbidities.

The AASLD recommends that patients with HCC at BCLC early stage or beyond undergo non-contrast chest CT to assess metastatic disease. However, it advises against the routine use of positron emission tomography (PET) and bone scans for staging, citing their low sensitivity for detecting HCC.[55] In contrast, the KLCA-NCC suggests that PET, chest CT, and bone scans may be used for staging in specific scenarios, such as prior to treatment with curative intent or when extrahepatic metastasis of HCC is suspected.

TREATMENT

Although the BCLC staging system has long been the dominant framework for treatment-guided staging of HCC, many Asia-Pacific experts do not fully agree with its principles (Fig. 1). The BCLC system, particularly in its recommendations for surgical resection, transarterial treatment, and other locoregional therapies, is often viewed as more conservative than Asian guidelines such as the KLCA-NCC, APASL, JSH, and TLCA. Asian guidelines generally adopt a more aggressive approach, favoring surgical resection, transarterial chemoembolization (TACE), and TACE-based combined treatments even for more advanced tumors.

Resection and transplantation

Surgical resection is recommended as the first-line treatment for patients with localized HCC lesions but without cirrhosis. However, guidelines vary in defining the optimal candidates for surgery. For example, guidelines adhering to the BCLC staging system recommend resection only for patients with solitary tumors but no evidence of portal hypertension. In contrast, the KLCA-NCC guidelines recommend resection for patients with up to three intrahepatic tumors without vascular invasion, provided that liver function is well preserved. Moreover, resection is conditionally permitted even for small single HCC with vascular invasion. Similarly, the JSH guidelines recommend resection for patients with HCC, regardless of tumor size, provided they have up to three tumors and Child-Pugh class A liver function. In addition, under the same tumor conditions, resection is more selectively permitted in patients with Child-Pugh class B liver function.

Resection has been demonstrated to provide the greatest benefit for single HCC in patients without cirrhosis, accounting for approximately 5% of cases in Western countries and 40% in Asia.[56,57] Recent studies have reported that postoperative mortality after HCC resection is low (less than 1-3%). Moreover, the 5-year overall survival and disease-free survival rates range from 46.0-69.5% and 23.0-56.3%, respectively.[58,59] Advances in surgical techniques, perioperative care, and patient selection have further enhanced outcomes for surgical resection in patients with cirrhosis.[60] The latest AASLD guidelines underscore the role of surgical resection in select patients with multifocal HCC beyond BCLC stage A criteria, supported by findings from recent studies in Western countries.[61,62] Similarly, the KLCA-NCC guidelines suggest that hepatic resection may be consid-

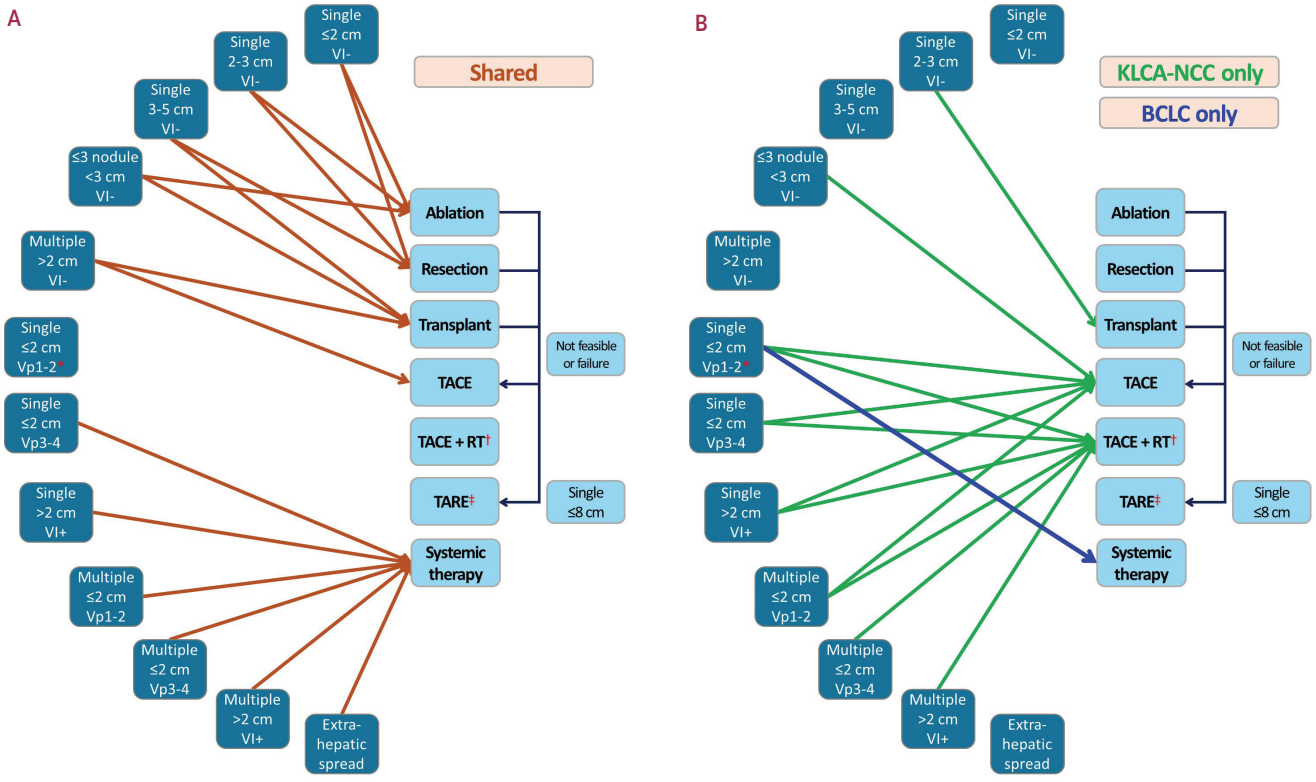

Figure 1. Comparison of first-line treatment allocation between the Korean Liver Cancer Association-National Cancer Center of Korea (KLCA-NCC) and Barcelona Clinic Liver Cancer (BCLC) guidelines. (A) Shared pathways and (B) KLCA-NCC and BCLC pathways shown separately. VI, vascular invasion; Vp1, tumor thrombus in the segmental branches of the PV; Vp2, tumor thrombus in the second-order branches of the PV; Vp3, tumor thrombus in the first-order branches of the PV; Vp4, tumor thrombus in the main trunk of the PV and/or branches of the PV contralateral to the primarily involved lobe; TACE, transarterial chemoembolization; RT, radiotherapy; TARE, transarterial radioembolization; PV, portal vein. *KLCA-NCC recommends surgical resection as an alternative option. †KLCA-NCC recommends combination treatment of conventional TACE plus EBRT for certain cases of hepatocellular carcinoma (HCC) with vascular invasion. ‡KLCA-NCC recommends transarterial radioembolization for single HCC with Vp1-2 or without VI, as well as for multiple localized HCC without VI, as an alternative option.

ered for HCC cases with invasion into the portal vein, hepatic vein, or bile duct, provided that the main portal trunk is not involved and liver function is preserved. This recommendation is based on evidence from several retrospective studies.[63-66]

Liver transplantation (LT) is consistently recommended across international guidelines as the preferred treatment for HCC within the Milan criteria, defined as a single tumor ≤5 cm or up to three nodules, each ≤3 cm, when resection is not feasible.[67,68] Owing to the excellent outcomes observed in patients meeting these criteria, many guidelines also suggest considering expanded criteria for patients with a large tumor burden. The expanded criteria include the University of California, San Francisco criteria with an 81% 5-year survival rate, the up-to-seven criteria with a 71% 5-year survival rate, and the Kyoto criteria with a 65% 5-year survival rate.[69-71]

Notable regional differences exist regarding the availability of allografts and allocation protocols for LT. In Korea, patients with HCC represent only 2-5% of all deceased donor LT cases. An European study found that prolonged waiting times for transplantation lead to up to 20% of patients being delisted because of tumor progression.[71] To mitigate this issue, bridging therapies (aimed at reducing waiting list dropout rates) and downstaging therapies (targeting patients initially beyond standard transplant criteria but potentially eligible for LT) have been extensively studied and require global consensus.[72] In the United States, patients within Milan criteria or those downstaged to within Milan criteria using the United Network for Organ Sharing downstaging criteria are eligible for an exception score after a mandatory 6-month waiting period.[73] The KLCA-NCC recommends LT for patients whose tumor stage has been successfully downstaged to meet Milan criteria through locoregional therapies such as TACE or radiofrequency ablation (RFA), as these patients demonstrate outcomes comparable to those originally within the Milan criteria. However, other Asian guidelines do not universally adopt downstaging strategies or expanded criteria for LT, reflecting the variability in regional approaches to transplantation.

The AASLD and BSG currently suggest considering adjuvant therapy with atezolizumab plus bevacizumab for patients at high risk of recurrence after liver resection or local ablation. However, these recommendations are expected to be revised because of the recent inability of the IMbrave050 trial to demonstrate clear superiority in immunotherapy groups.[73] In contrast, the APASL has stated that recommending adjuvant therapy with atezolizumab plus bevacizumab at this stage is premature. Meanwhile, the KLCA-NCC suggests that adjuvant immunotherapy with cytokine-induced killer cells should be considered following curative treatment, although further multinational validation studies are needed.[74]

Locoregional therapies

RFA is recommended as an alternative to surgical resection for patients with a solitary tumor and good hepatic function. Most guidelines indicate that RFA provides comparable outcomes to resection in patients with single-nodular HCC ≤3 cm. However, the AASLD has expanded its recommendations to include local ablative therapies, such as RFA, for patients with single-nodular HCC ≤5 cm who are either ineligible for or decline surgical treatment. The EASL further highlights microwave ablation as a promising modality for local tumor control and improved survival. In addition, the EASL presents studies demonstrating that combining RFA with TACE improves survival outcomes compared with RFA alone in patients with 3-5 cm sized HCCs when surgical resection is not an option.[74]

TACE is the primary treatment option for patients with multinodular HCC without vascular invasion, exploiting the arterial blood supply of the HCC in contrast to the portal venous blood flow of the surrounding normal liver. It can be performed using either lipiodol (conventional TACE, cTACE) or drug-eluting beads (DEB-TACE). The KLCA-NCC additionally recommends TACE for patients with portal vein invasion, with or without the addition of external beam radiation therapy (EBRT).[75,76] Both the EASL and KLCA-NCC suggest DEB-TACE as an alternative to cTACE for intermediate-stage HCC. Transarterial radioembolization (TARE), also known as selective internal radiation therapy, has been increasingly adopted, leading to significant updates to several guidelines. The BCLC now includes TARE as a treatment option for single HCCs ≤8 cm after the failure of initial treatment for BCLC stage 0/A HCC.[74] The AASLD also recommends TARE as an alternative to TACE for treatment of patients with BCLC stage B HCC. The APASL has further expanded the indications for TARE as a locoregional therapy for unresectable HCC. The KLCA-NCC highlights that TARE provides a better quality of life and a lower incidence of post-embolization syndrome than TACE.[77] Meanwhile, the TLCA suggests considering TACE alone or in combination with sorafenib or lenvatinib for unresectable intermediate-stage HCC in patients meeting the up to 11 criteria for BCLC stage B disease.[78,79]

The EASL recommends a conservative approach for EBRT, reserving it for selected cases. In contrast, the BSG considers

EBRT a viable option for tumor ablation in patients who are unsuitable for surgery or conventional ablative techniques. The KLCA-NCC provides the broadest guidance and recommends EBRT as an alternative for patients with HCC who are not candidates for hepatic resection, transplantation, local ablation, or TACE. The AASLD highlights findings from a Korean clinical trial comparing proton beam therapy (PBT) and RFA in patients with recurrent or residual HCC, suggesting that PBT may be considered an alternative to RFA in specific cases.[80,81]

Systemic therapies

Systemic therapy is primarily reserved for patients with unresectable HCC who are not candidates for locoregional treatment, including those with advanced-stage disease. With the development of several new agents, recent guidelines from various regions have either provided more detailed recommendations for systemic therapy or issued separate updates on this topic.[82,83] Recent studies on first-line systemic therapies demonstrating significant survival benefits have led to the inclusion of combinations such as atezolizumab plus bevacizumab or durvalumab plus tremelimumab in the updated guidelines.[84] In contrast, older guidelines primarily listed tyrosine kinase inhibitors as first-line options, despite emerging evidence suggesting that treatment efficacy may vary based on HCC etiology.

Most guidelines recommend atezolizumab plus bevacizumab and durvalumab plus tremelimumab as the preferred first-line therapies for HCC. The APASL additionally includes nivolumab plus ipilimumab, sintilimab plus IBI305, and camrelizumab plus rivoceranib (apatinib) as preferred first-line options, depending on tolerance to adverse events.[18,85,86] However, guidelines such as the BSG highlight that sintilimab plus IBI305 and camrelizumab plus rivoceranib have not been extensively evaluated in non-hepatitis B virus populations outside Asia, limiting their use as first-line therapies globally. Owing to the high risk of gastrointestinal bleeding, the AASLD recommends that patients considered for atezolizumab plus bevacizumab treatment undergo esophagogastroduodenoscopy (EGD) to screen for high-risk stigmata of variceal or other gastrointestinal bleeding. Similarly, the KLCA-NCC advises evaluating patients at high risk of bleeding for gastroesophageal varices through EGD and managing these risks before initiating atezolizumab plus bevacizumab treatment. All guidelines also propose alternative first-line regimens such as lenvatinib or sorafenib for patients ineligible for atezolizumab plus bevacizumab or durvalumab plus tremelimumab treatment. In the second-line setting, following progression to first-line atezolizumab plus bevacizumab, lenvatinib has shown better outcomes than sorafenib. However, further prospective studies are required to validate these findings.[87,88]

The concept of TACE refractoriness has been proposed to address insufficient responses to TACE due to tumor biology. The KLCA-NCC defines TACE refractoriness as the absence of an objective response after two or more sessions of on-demand cTACE within 6 months, the development of vascular invasion, or the occurrence of extrahepatic metastasis. The AASLD and most Asian guidelines have addressed the concept of TACE refractoriness and recommend transitioning to systemic therapy for patients with intermediate-stage HCC that is either refractory to TACE or deemed unsuitable for further TACE. The JSH provides detailed descriptions of TACE unsuitability and refractoriness while presenting various treatment strategies, including combined therapies such as TACE plus systemic treatment. However, other guidelines have not yet addressed the concept of TACE refractoriness.[89,90]

The ASCO and AGA have also highlighted concerns regarding health equity and disparities. The ASCO has emphasized the importance of considering the low rates of treatment with systemic therapy, disparities in access to care and clinical trials, and differences in outcomes within the context of this clinical practice guideline.

CONCLUSION

The current guidelines for HCC management are broadly similar, although some discrepancies persist in surveillance and treatment allocation recommendations. Recommendations from the three main regions (Asia, Europe, and the United States) are influenced by geographic variations in disease prevalence and biology (e.g., the higher prevalence of hepatitis B in some regions and differing rates of steatotic liver disease across regions) as well as differences in resources, such as treatment accessibility, financial constraints, and organ availability, for LT. While these regional differences pose challenges in establishing a global consensus, the gap between Eastern and Western approaches has narrowed in recent years. Efforts to understand and bridge these regional disparities are crucial to foster international collaboration and advance HCC management. Physicians and policymakers must consider these factors when managing patients with HCC and developing policies and guidelines to ensure optimal and equitable care.

Conflicts of Interest

The authors have no conflicts of interest to disclose.

Ethics Statement

This review article is fully based on articles which have already been published and did not involve additional patient participants. Therefore, IRB approval is not necessary.

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REFERENCES

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229-263.
2. Goutté N, Sogni P, Bendersky N, Barbare JC, Falissard B, Farges O. Geographical variations in incidence, management and survival of hepatocellular carcinoma in a Western country. J Hepatol 2017;66:537-544.
3. Toh MR, Wong EYT, Wong SH, Ng AWT, Loo LH, Chow PK, et al. Global epidemiology and genetics of hepatocellular carcinoma. Gastroenterology 2023;164:766-782.
4. Giannini EG, Farinati F, Ciccarese F, Pecorelli A, Rapaccini GL, Di Marco M, et al. Prognosis of untreated hepatocellular carcinoma. Hepatology 2015;61:184-190.
5. Yilma M, Xu RH, Saxena V, Muzzin M, Tucker LY, Lee J, et al. Survival outcomes among patients with hepatocellular carcinoma in a large integrated US health system. JAMA Netw Open 2024;7:e2435066.
6. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017;11:317-370.
7. European Association for the Study of the Liver. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
8. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29 Suppl 4:iv238-iv255.
9. Korean Liver Cancer Association (KLCA), National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol 2022;28:583-705.
10. Su GL, Altayar O, O'Shea R, Shah R, Estfan B, Wenzell C, et al. AGA clinical practice guideline on systemic therapy for hepatocellular carcinoma. Gastroenterology 2022;162:920-934.
11. Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, et al. AASLD practice guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology 2023;78:1922-1965.
12. National Comprehensive Cancer Network (NCCN). NCCN guidelines for hepatocellular carcinoma ver. 4 [Internet]. Plymouth Meeting (US): NCCN; [cited 2025 Jan 15]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1514.
13. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. Clinical practice guidelines we can trust. Washington DC: National Academies Press, 2011.
14. Yu SJ. A concise review of updated guidelines regarding the management of hepatocellular carcinoma around the world: 2010-2016. Clin Mol Hepatol 2016;22:7-17.
15. Kudo M, Kawamura Y, Hasegawa K, Tateishi R, Kariyama K, Shiina S, et al. Management of hepatocellular carcinoma in Japan: JSH consensus statements and recommendations 2021 update. Liver Cancer 2021;10:181-223.
16. Hasegawa K, Takemura N, Yamashita T, Watadani T, Kaibori M, Kubo S, et al. Clinical practice guidelines for hepatocellular carcinoma: The Japan Society of Hepatology 2021 version (5th JSH-HCC guidelines). Hepatol Res 2023;53:383-390.
17. Teng W, Wang HW, Lin SM; Diagnosis Group and Systemic Therapy Group of TLCA. Management consensus guidelines for hepatocellular carcinoma: 2023 update on surveillance, diagnosis, systemic treatment, and posttreatment monitoring by the Taiwan Liver Cancer Association and the Gastroenterological Society of Taiwan. Liver Cancer 2024;13:468-486.
18. Lau G, Obi S, Zhou J, Tateishi R, Qin S, Zhao H, et al. APASL clinical practice guidelines on systemic therapy for hepatocellular carcinoma-2024. Hepatol Int 2024;18:1661-1683.
19. Kudo M, Han KH, Ye SL, Zhou J, Huang YH, Lin SM, et al. A changing paradigm for the treatment of intermediate-stage hepatocellular carcinoma: Asia-Pacific Primary Liver Cancer Expert consensus statements. Liver Cancer 2020;9:245-260.
20. Suddle A, Reeves H, Hubner R, Marshall A, Rowe I, Tiniakos D, et al. British Society of Gastroenterology guidelines for the management of hepatocellular carcinoma in adults. Gut 2024;73:1235-1268.
21. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76:681-693.
22. Gordan JD, Kennedy EB, Abou-Alfa GK, Beal E, Finn RS, Gade TP, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline update. J Clin Oncol 2024;42:1830-1850.
23. Croswell JM, Ransohoff DF, Kramer BS. Principles of cancer screening: lessons from history and study design issues. Semin Oncol 2010;37:202-215.
24. Kanwal F, Singal AG. Surveillance for hepatocellular carcinoma: current best practice and future direction. Gastroenterology 2019;157:54-64.
25. Parikh ND, Singal AG, Hutton DW, Tapper EB. Cost-effectiveness of hepatocellular carcinoma surveillance: an assessment of benefits and harms. Am J Gastroenterol 2020;115:1642-1649.
26. Papatheodoridis G, Dalekos G, Sypsa V, Yurdaydin C, Buti M, Goulis J, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016;64:800-806.
27. Orci LA, Sanduzzi-Zamparelli M, Caballol B, Sapena V, Colucci N, Torres F, et al. Incidence of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. Clin Gastroenterol Hepatol 2022;20:283-292.e10.
28. Chong N, Schoenberger H, Yekkaluri S, Fetzer DT, Rich NE, Yokoo T,

et al. Association between ultrasound quality and test performance for HCC surveillance in patients with cirrhosis: a retrospective cohort study. Aliment Pharmacol Ther 2022;55:683-690.
29. Fetzer DT, Browning T, Xi Y, Yokoo T, Singal AG. Associations of ultrasound LI-RADS visualization score with examination, sonographer, and radiologist factors: retrospective assessment in over 10,000 examinations. AJR Am J Roentgenol 2022;218:1010-1020.
30. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. Gastroenterology 2018;154:1706-1718.e1.
31. Colli A, Nadarevic T, Miletic D, Giljaca V, Fraquelli M, Štimac D, et al. Abdominal ultrasound and alpha-foetoprotein for the diagnosis of hepatocellular carcinoma in adults with chronic liver disease. Cochrane Database Syst Rev 2021;4:CD013346.
32. Yuen MF, Lai CL. Serological markers of liver cancer. Best Pract Res Clin Gastroenterol 2005;19:91-99.
33. Choi J, Tayob N, Lim YS. Detecting early hepatocellular carcinoma in patients with chronic hepatitis B using longitudinal α-fetoprotein screening. Clin Gastroenterol Hepatol 2023;21:1590-1597.
34. Singal A, Volk ML, Waljee A, Salgia R, Higgins P, Rogers MA, et al. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30:37-47.
35. Gopal P, Yopp AC, Waljee AK, Chiang J, Nehra M, Kandunoori P, et al. Factors that affect accuracy of α-fetoprotein test in detection of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2014;12:870-877.
36. Di Bisceglie AM, Sterling RK, Chung RT, Everhart JE, Dienstag JL, Bonkovsky HL, et al. Serum alpha-fetoprotein levels in patients with advanced hepatitis C: results from the HALT-C Trial. J Hepatol 2005;43:434-441.
37. Zhou XD, Tang ZY, Fan J, Zhou J, Wu ZQ, Qin LX, et al. Intrahepatic cholangiocarcinoma: report of 272 patients compared with 5,829 patients with hepatocellular carcinoma. J Cancer Res Clin Oncol 2009;135:1073-1080.
38. Gupta P, Soundararajan R, Patel A, Kumar-M P, Sharma V, Kalra N. Abbreviated MRI for hepatocellular carcinoma screening: a systematic review and meta-analysis. J Hepatol 2021;75:108-119.
39. Park HJ, Kim SY, Singal AG, Lee SJ, Won HJ, Byun JH, et al. Abbreviated magnetic resonance imaging vs ultrasound for surveillance of hepatocellular carcinoma in high-risk patients. Liver Int 2022;42:2080-2092.
40. Kim SC, Kim DW, Cho EJ, Lee JY, Kim J, Kwon C, et al. A circulating cell-free DNA methylation signature for the detection of hepatocellular carcinoma. Mol Cancer 2023;22:164.
41. Nathani P, Gopal P, Rich N, Yopp A, Yokoo T, John B, et al. Hepatocellular carcinoma tumour volume doubling time: a systematic review and meta-analysis. Gut 2021;70:401-407.
42. Barbara L, Benzi G, Gaiani S, Fusconi F, Zironi G, Siringo S, et al. Natural history of small untreated hepatocellular carcinoma in cirrhosis: a multivariate analysis of prognostic factors of tumor growth rate and patient survival. Hepatology 1992;16:132-137.
43. Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, et al. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol 2010;53:291-297.
44. Trinchet JC, Chaffaut C, Bourcier V, Degos F, Henrion J, Fontaine H, et al. Ultrasonographic surveillance of hepatocellular carcinoma in cirrhosis: a randomized trial comparing 3- and 6-month periodicities. Hepatology 2011;54:1987-1997.
45. Singal AG, Sanduzzi-Zamparelli M, Nahon P, Ronot M, Hoshida Y, Rich N, et al. International Liver Cancer Association (ILCA) white paper on hepatocellular carcinoma risk stratification and surveillance. J Hepatol 2023;79:226-239.
46. Wang JH, Chang KC, Kee KM, Chen PF, Yen YH, Tseng PL, et al. Hepatocellular carcinoma surveillance at 4- vs. 12-month intervals for patients with chronic viral hepatitis: a randomized study in community. Am J Gastroenterol 2013;108:416-424.
47. Forner A, Vilana R, Ayuso C, Bianchi L, Solé M, Ayuso JR, et al. Diagnosis of hepatic nodules 20 mm or smaller in cirrhosis: prospective validation of the noninvasive diagnostic criteria for hepatocellular carcinoma. Hepatology 2008;47:97-104.
48. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology 2008;47:82-89.
49. Park MK, Lee DH, Hur BY, Lee HC, Lee YB, Yu SJ, et al. Effectiveness of US surveillance of hepatocellular carcinoma in chronic hepatitis B: US LI-RADS visualization score. Radiology 2023;307:e222106.
50. Rodgers SK, Fetzer DT, Gabriel H, Seow JH, Choi HH, Maturen KE, et al. Role of US LI-RADS in the LI-RADS algorithm. Radiographics 2019;39:690-708.
51. Haimerl M, Verloh N, Zeman F, Fellner C, Nickel D, Lang SA, et al. Gd-EOB-DTPA-enhanced MRI for evaluation of liver function: comparison between signal-intensity-based indices and T1 relaxometry. Sci Rep 2017;7:43347.
52. Roberts LR, Sirlin CB, Zaiem F, Almasri J, Prokop LJ, Heimbach JK, et al. Imaging for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. Hepatology 2018;67:401-421.
53. Mitchell DG, Bruix J, Sherman M, Sirlin CB. LI-RADS (Liver Imaging Reporting and Data System): summary, discussion, and consensus of the LI-RADS Management Working Group and future directions. Hepatology 2015;61:1056-1065.
54. Qu C, Wang Y, Wang P, Chen K, Wang M, Zeng H, et al. Detection of early-stage hepatocellular carcinoma in asymptomatic HBsAg-seropositive individuals by liquid biopsy. Proc Natl Acad Sci U S A 2019;116:6308-6312.
55. Chotipanich C, Kunawudhi A, Promteangtrong C, Tungsuppawattanakit P, Sricharunrat T, Wongsa P. Diagnosis of hepatocellular carcinoma using C11 choline PET/CT: comparison with F18 FDG, contrastenhanced MRI and MDCT. Asian Pac J Cancer Prev 2016;17:3569-3573.
56. Lang H, Sotiropoulos GC, Dömland M, Frühauf NR, Paul A, Hüsing J, et al. Liver resection for hepatocellular carcinoma in non-cirrhotic liver without underlying viral hepatitis. Br J Surg 2005;92:198-202.
57. Andreou A, Vauthey JN, Cherqui D, Zimmitti G, Ribero D, Truty MJ, et al. Improved long-term survival after major resection for hepatocellular carcinoma: a multicenter analysis based on a new definition of major hepatectomy. J Gastrointest Surg 2013;17:66-77; discussion p.77.
58. Lee EC, Kim SH, Park H, Lee SD, Lee SA, Park SJ. Survival analysis after liver resection for hepatocellular carcinoma: a consecutive cohort of 1002 patients. J Gastroenterol Hepatol 2017;32:1055-1063.
59. Torzilli G, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G, et al. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations? An observational study of the HCC East-West Study Group. Ann Surg 2013;257:929-937.
60. Makuuchi M, Sano K. The surgical approach to HCC: our progress and results in Japan. Liver Transpl 2004;10 Suppl 1:S46-S52.
61. Hyun MH, Lee YS, Kim JH, Lee CU, Jung YK, Seo YS, et al. Hepatic resection compared to chemoembolization in intermediate- to advanced-stage hepatocellular carcinoma: a meta-analysis of high-quality studies. Hepatology 2018;68:977-993.
62. Tsilimigras DI, Mehta R, Paredes AZ, Moris D, Sahara K, Bagante F, et al. Overall tumor burden dictates outcomes for patients undergoing resection of multinodular hepatocellular carcinoma beyond the Milan criteria. Ann Surg 2020;272:574-581.
63. Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol 2016;65:938-943.
64. Zhang ZY, Dong KS, Zhang EL, Zhang LW, Chen XP, Dong HH. Resection

might be a meaningful choice for hepatocellular carcinoma with portal vein thrombosis: a systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e18362.
65. Govalan R, Lauzon M, Luu M, Ahn JC, Kosari K, Todo T, et al. Comparison of surgical resection and systemic treatment for hepatocellular carcinoma with vascular invasion: National Cancer Database analysis. Liver Cancer 2021;10:407-418.
66. Kim DS, Kim BW, Hatano E, Hwang S, Hasegawa K, Kudo A, et al. Surgical outcomes of hepatocellular carcinoma with bile duct tumor thrombus: a Korea-Japan multicenter study. Ann Surg 2020;271:913-921.
67. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-699.
68. Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. Liver Transpl 2011;17 Suppl 2:S44-S57.
69. Yao FY, Xiao L, Bass NM, Kerlan R, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. Am J Transplant 2007;7:2587-2596.
70. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009;10:35-43.
71. Kaido T, Ogawa K, Mori A, Fujimoto Y, Ito T, Tomiyama K, et al. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. Surgery 2013;154:1053-1060.
72. Hwang SY, Choi H, Jeon W, Kim RG. Multidisciplinary approaches to downstaging hepatocellular carcinoma: present and future. J Liver Cancer 2024;24:171-177.
73. Zendel A, Watkins R, Moon AM, Gerber DA, Barritt AS 4th, Desai CS. Changing opportunities for liver transplant for patients with hepatocellular carcinoma. Clin Transplant 2022;36:e14609.
74. Lee JH, Lee JH, Lim YS, Yeon JE, Song TJ, Yu SJ, et al. Adjuvant immunotherapy with autologous cytokine-induced killer cells for hepatocellular carcinoma. Gastroenterology 2015;148:1383-1391.e6.
75. Chung GE, Lee JH, Kim HY, Hwang SY, Kim JS, Chung JW, et al. Transarterial chemoembolization can be safely performed in patients with hepatocellular carcinoma invading the main portal vein and may improve the overall survival. Radiology 2011;258:627-634.
76. Yoon SM, Ryoo BY, Lee SJ, Kim JH, Shin JH, An JH, et al. Efficacy and safety of transarterial chemoembolization plus external beam radiotherapy vs sorafenib in hepatocellular carcinoma with macroscopic vascular invasion: a randomized clinical trial. JAMA Oncol 2018;4:661-669.
77. Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. J Clin Oncol 2018;36:1913-1921.
78. Peng Z, Fan W, Zhu B, Wang G, Sun J, Xiao C, et al. Lenvatinib combined with transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma: a phase III, Randomized clinical trial (LAUNCH). J Clin Oncol 2023;41:117-127.
79. Hung YW, Lee IC, Chi CT, Lee RC, Liu CA, Chiu NC, et al. Redefining tumor burden in patients with intermediate-stage hepatocellular carcinoma: the seven-eleven criteria. Liver Cancer 2021;10:629-640.
80. Kim TH, Koh YH, Kim BH, Kim MJ, Lee JH, Park B, et al. Proton beam radiotherapy vs. radiofrequency ablation for recurrent hepatocellular carcinoma: a randomized phase III trial. J Hepatol 2021;74:603-612.
81. Bae SH, Jang WI, Mortensen HR, Weber B, Kim MS, Høyer M. Recent update of proton beam therapy for hepatocellular carcinoma: a systematic review and meta-analysis. J Liver Cancer 2024;24:286-302.
82. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med 2020;382:1894-1905.
83. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid 2022;1:EVIDoa2100070.
84. Zanuso V, Tesini G, Valenzi E, Rimassa L. New systemic treatment options for advanced cholangiocarcinoma. J Liver Cancer 2024;24:155-170.
85. Ren Z, Xu J, Bai Y, Xu A, Cang S, Du C, et al. Sintilimab plus a bevacizumab biosimilar (IBI305) versus sorafenib in unresectable hepatocellular carcinoma (ORIENT-32): a randomised, open-label, phase 2-3 study. Lancet Oncol 2021;22:977-990.
86. Qin S, Chan SL, Gu S, Bai Y, Ren Z, Lin X, et al. Camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable hepatocellular carcinoma (CARES-310): a randomised, open-label, international phase 3 study. Lancet 2023;402:1133-1146.
87. Persano M, Casadei-Gardini A, Tada T, Suda G, Shimose S, Kudo M, et al. Lenvatinib versus sorafenib second-line therapy in patients with hepatocellular carcinoma progressed to atezolizumab plus bevacizumab: a retrospective real-world study. Oncology. 2024 Oct 11. doi: 10.1159/000541018 [Epub ahead of print].
88. Chon YE, Kim DY, Kim MN, Kim BK, Kim SU, Park JY, et al. Sorafenib vs. Lenvatinib in advanced hepatocellular carcinoma after atezolizumab/bevacizumab failure: a real-world study. Clin Mol Hepatol 2024;30:345-359.
89. Frantz S, Matsuoka L, Vaheesan K, Petroziello M, Golzarian J, Wang E, et al. Multicenter evaluation of survival and toxicities of hepatocellular carcinoma following radioembolization: analysis of the RESiN registry. J Vasc Interv Radiol 2021;32:845-852.
90. Adhoute X, Penaranda G, Naude S, Raoul JL, Perrier H, Bayle O, et al. Retreatment with TACE: the ABCR SCORE, an aid to the decision-making process. J Hepatol 2015;62:855-862.