Received: 25 November 2024 | Revised: 10 April 2025 | Accepted: 11 April 2025

DOI: 10.3322/caac.70018

REVIEW ARTICLE

Advances in the treatment of hepatocellular carcinoma: An overview of the current and evolving therapeutic landscape for clinicians

Dimitrios Moris MD, MSc, PhD[1] | Alessandro Martinino MD[2] | Sarah Schiltz BS[3,4,5] | Peter J. Allen MD[1] | Andrew Barbas MD[2] | Debra Sudan MD[2] | Lindsay King MD, MPH[6] | Carl Berg MD[6] | Charles Kim MD[7] | Mustafa Bashir MD[7] | Manisha Palta MD[8] | Michael A. Morse MD, MHS[9] | Michael E. Lidsky MD[1]

[1]Division of Surgical Oncology, Department of Surgery, Duke University Medical Center, Durham, North Carolina, USA

[2]Division of Abdominal Transplantation, Department of Surgery, Duke University Medical Center, Durham, North Carolina, USA

[3]Patient Advocate Steering Committee, National Cancer Institute Hepatobiliary Task Force, Los Gatos, California, USA

[4]Blue Faery, Simi Valley, California, USA

[5]Cancer CAREpoint, Los Gatos, California, USA

[6]Division of Gastroenterology and Hepatology, Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA

[7]Department of Radiology, Duke University Medical Center, Durham, North Carolina, USA

[8]Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina, USA

[9]Division of Medical Oncology, Department of Medicine, Duke University Medical Center, Durham, North Carolina, USA

Correspondence
Michael E. Lidsky, Division of Surgical Oncology, Department of Surgery, Duke University Medical Center, Box 3966, 10 Bryan Searle Drive, 466G Seeley G. Mudd Building, Durham, NC 27710, USA.
Email: Michael.lidsky@duke.edu

Abstract

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third leading cause of cancer-related death worldwide. Contemporary advances in systemic and locoregional therapies have led to changes in peer-reviewed guidelines regarding systemic therapy as well as the possibility of downstaging disease that may enable some patients with advanced disease to ultimately undergo partial hepatectomy or transplantation with curative intent. This review focuses on all modalities of therapy for HCC, guided by modern-day practice-changing randomized data where available. The surgical management of HCC, including resection and transplantation, both of which have evolving criteria for what is considered biologically resectable and transplantable, as well as locoregional therapy (i.e., therapeutic embolization, ablation, radiation, and hepatic arterial infusion), are discussed. Historical and modern-day practice-changing trials evaluating immunotherapy with targeted therapies for advanced disease, as well as adjuvant systemic therapy, are also summarized. In addition, this article examines the critical dimension of toxicities and patient-oriented considerations to ensure a comprehensive and balanced discourse on treatment implications.

KEYWORDS
ablation, external beam radiation, hepatectomy, immunotherapy, liver transplantation, multimodal therapy, patient selection, toxicity, transarterial therapies, tyrosine kinase inhibitor

INTRODUCTION

The incidence of hepatocellular carcinoma (HCC) is rising, especially in younger populations.[1] HCC most commonly develops in the setting of chronic liver disease, in which longstanding inflammatory states predispose patients to malignancy.[2] Although viral hepatitis and alcohol remain the primary etiology of chronic liver disease worldwide, *metabolic dysfunction-associated steatohepatitis* (MASH) is an emerging cause of cirrhosis and HCC in the United States because of an increase in the prevalence of obesity and metabolic syndrome.[2]

Surgical treatment provides the best opportunity for cure in patients with HCC provided they are eligible for resection or liver transplantation (LT). Unfortunately, a significant number of patients with HCC is diagnosed at advanced stages, managed with mostly palliative locoregional and/or systemic therapies, which offer symptom relief and disease control but not a cure.[3]

Approximately 50% of patients with HCC receive systemic therapies, and, until recently, the standard of care remained multikinase inhibitors in the first-line and second-line settings.[4] In the past 5 years, however, immune checkpoint inhibitors (ICIs) have revolutionized the management of patients with advanced HCC. The advent of more effective systemic therapies, often paired with locoregional therapies, has facilitated prolonged survival among patients with metastatic as well as locally advanced disease and has allowed for some patients to undergo surgical intervention when radical surgery previously would not have been an option.

Given the complexities and nuances of HCC management, patients are ideally treated in a multidisciplinary setting in which surgeons, medical oncologists, radiation oncologists, interventional radiologists, as well as hepatologists collaborate to deliver optimal care to achieve optimal outcomes. It also remains critical that treatment paradigms take into consideration patient-and tumor-related factors, such as performance status, extent of disease, and liver dysfunction, each of which are primary drivers of morbidity and mortality. In the context of the rapidly evolving surgical and systemic therapeutic landscape and treatment guidelines for HCC, this comprehensive review of multimodal management strategies for patients with HCC provides a valuable resource for all clinicians.

EPIDEMIOLOGY

Liver cancer is the sixth most common cancer and the third leading cause of cancer-specific mortality worldwide.[5] In 2022, liver cancer accounted for approximately 866,136 cases and 758,725 deaths globally,[5] with an estimated 29,840 new cases and related deaths expected in the United States in 2024.[6] Throughout the world, HCC is the dominant type of liver cancer, accounting for approximately 75% of all cases.[7,8] The highest rates of HCC diagnosis are among individuals aged 60–70 years, with a higher prevalence in males.[7] The incidence and mortality rates of HCC differ across the world and among ethnic groups, a variance largely linked to the geographic distribution and the age at which people are exposed to key risk factors.[9] East Asian and African populations witness the highest incidence and death rates from HCC. However, the global prevalence of HCC has transitioned over time from areas with low-to-moderate now to include areas with high sociodemographic indices.[10,11] This transition suggests a shift in the leading causes of HCC from viral to nonviral etiologies.[12] Consequently, both incidence and mortality rates of HCC are increasing in several European nations and the United States. In the United States specifically, HCC incidence has risen from 2.38 to 3.09 per 100,000 women from 2001 to 2020 and from 7.32 to 9.82 per 100,000 men over the same period. In addition, the number of new cases of liver cancer per year is predicted to increase by 55% between 2020 and 2040 globally, with a projected 1.4 million people diagnosed in 2040. Furthermore, it is predicted that 1.3 million people could die from liver cancer in 2040, which is 56% higher than in 2020.[13–16]

RISK FACTORS FOR HCC

More than 90% of HCC cases develop amidst chronic inflammatory liver disease.[15] Cirrhosis, regardless of its etiology, represents the primary risk factor for HCC; and HCC, which has an annual incidence of 1%–6% in the cirrhotic population, is the foremost cause of mortality in this population.[17–19]

Viral hepatitis is the most common risk factor for HCC. Worldwide, it is estimated that over 350 million people have chronic infections caused by hepatitis B (HBV) and hepatitis C virus (HCV), with 80%–90% of these individuals unaware of their infection status[20] and thus at an unappreciated risk for HCC.[15,21] In Asia and Africa, approximately 60% of HCC cases are attributable to HBV infection, whereas, in Western regions, this figure remains approximately 20%.[12] Chronic HCV infection is the most prevalent precursor to HCC in regions such as North America, Europe, and Japan.[12] Although the majority of cases of HCC are associated with advanced fibrotic liver disease (bridging fibrosis or cirrhosis), HBV-associated HCC may occur in the absence of advanced fibrosis, an observation that affects screening strategies for patients with chronic HBV disease.

Alcohol-related liver disease accounts for 20% of HCC cases[22] and is an independent risk factor for HCC.[23,24] Furthermore, alcohol can enhance the effects of other risk factors, such as viral hepatitis, leading to an earlier onset of liver cancer.[20] Patients diagnosed with HCC because of alcohol have the lowest survival rate compared with those who have HCC caused by other factors (median survival, 6 vs. 8–10 months).[25,26]

MASH has seen a notable rise in its association with HCC since 2010. Currently, MASH accounts for 15%–20% of HCC cases in Western countries.[27] HCC without cirrhosis occurs more frequently in cases related to MASH compared with other causes. Specifically, 39% of HCC cases associated with MASH arise without cirrhosis, in contrast to 22% for HBV, 6% for HCV, and 9% for alcohol-related liver disease.[2,28] For those patients without HBV (see above) in this cohort, HCC without cirrhosis is still most often identified in the

milieu of advanced fibrosis. Studies have demonstrated that metabolic dysfunction-associated steatotic liver disease is more prevalent in men than in women during the premenopausal stage; however, its prevalence is higher in postmenopausal women.[29]

Iron overload and *aflatoxin* are additional though less common risk factors for HCC. Iron deposition can result in oxidative damage to cells and ferroptosis,[30] and the most common disease is hereditary hemochromatosis,[31–33] which is linked to a heightened risk of developing HCC, with past estimates suggesting the risk could be up to 200 times greater.[34] Aflatoxin is a carcinogenic substance produced by *Aspergillus* mold. It is linked to 5%–28% of HCC cases worldwide and has a geographic prevalence that mirrors that of HBV. When both aflatoxin and HBV are present, the risk of developing HCC can increase by four to 10 times.[35,36]

SCREENING

Numerous professional organizations and societies[16,37–41] advocate for screening patients who are at risk, predominantly consisting of people with cirrhosis and those with chronic HBV infection in the absence of cirrhosis.[17,37,39–41] HCC screening mainly benefits those with compensated cirrhosis, classified as Child–Turcotte–Pugh (CTP) class A or B. For patients with advanced cirrhosis (CTP class C), screening is typically not recommended because of the absence of tolerable effective treatments, except for patients who are eligible for consideration of LT, in whom a tailored screening strategy may be appropriate. The effectiveness of HCC screening in patients with significant fibrosis but not cirrhosis is a topic of ongoing discussion. European guidelines advocate for screening in these cases, highlighting the challenge in precisely identifying the shift from advanced fibrosis to cirrhosis.[17] Although most guidelines limit HCC screening to certain groups of noncirrhotic patients with HBV, screening has been found to be cost-effective for patients who have HBV without cirrhosis if the annual incidence rate exceeds 0.2%.[17] In addition, screening is often deemed unnecessary for patients with competing liver or other diseases that shorten life expectancy to 12 months or less.[17,39–41]

Guidelines recommend biannual measurement of α-fetoprotein (AFP) in combination with ultrasound (US) for HCC surveillance because of its cost effectiveness, noninvasive nature, accessibility, reasonable accuracy, and patient tolerance.[37] The 2024 US Liver Imaging Reporting and Data System (LI-RADS) surveillance protocol advises interpreting radiologists to assign a score (US-1, US-2, or US-3) based on their observations and provide a corresponding follow-up imaging recommendation. Category US-1 refers to a US study without evidence of HCC. Category US-2 subthreshold indicates an observation measuring <10 mm and requires follow-up US in 3–6 months. Category US-3 describes an examination with observations measuring ≥10 mm, not definitely benign, including area(s) of parenchymal distortion or a new thrombus in the portal or hepatic vein, necessitating multiphase, contrast-enhanced imaging.[42] It should also be noted that patients with HCV cirrhosis who achieve a sustained virologic response after antiviral therapy, although they are considered cured from vital hepatitis, remain at high risk for HCC and thus should continue HCC surveillance indefinitely with biannual AFP measurement and liver US imaging.

DIAGNOSIS

Imaging has long been central to the care of patients at risk for, and/or with a diagnosis of, HCC because it is a critical part of surveillance, diagnosis, staging, treatment, and follow-up. Various technologies have extended the capabilities of imaging, including hepatobiliary contrast agents in magnetic resonance imaging (MRI) as well as intravenous contrast agents for US (Table 1). Importantly, HCC is the only liver tumor in which the classic imaging appearance is specific enough to forgo biopsy and proceed directly to treatment, and perhaps the most effective advances related to HCC imaging have been related to increases in spatial resolution, contrast enhancement, and knowledge of artifacts.

Imaging modalities

In the diagnostic assessment of people with cirrhosis who are at elevated risk for HCC, multidetector computed tomography (CT) is indispensable. The use of multiphase contrast-enhanced imaging, which includes late arterial, portal-venous, and delayed phases, is critical for accurate imaging diagnosis.[39] The defining imaging characteristics for the diagnosis of HCC on multidetector computed tomography are: nonrim arterial hyperenhancement during the late arterial phase and nonperipheral washout in the portal-venous and/or delayed phases.[43,44] This pattern mirrors the unique vascular alterations associated with hepatocarcinogenesis, in which tumor inflow relative to the remainder of the liver is increased through the hepatic arterial system and decreased through the portal venous system.

MRI is highly effective for detecting and characterizing lesions because of its superior contrast resolution and its ability to assess various tissue properties beyond vascularization.[45] It is the preferred imaging modality for characterizing suspicious nodules identified during the screening of high-risk patients.[45] A recent meta-analysis reported that pooled sensitivity and specificity of MRI for diagnosing HCC was 70% and 94%, respectively, regardless of tumor size.[46] Sensitivity is nearly 100% for lesions >2 cm, decreases to 58.3%–64.6% for lesions <2 cm, and is even lower for subcentimeter lesions.[47–50] Despite this, MRI generally outperforms CT for diagnosing HCC lesions <2 cm and has similar accuracy for lesions ≥2 cm.[51] In addition, MRI has seen substantial improvements in the past 5–10 years, with motion-robust techniques becoming more widely available. In addition, short temporal window imaging has led to more precise arterial phase timing as well as mitigation of artifacts related to fast transit of the contrast bolus. MRI is also helpful in distinguishing HCC from other common hypervascular lesions that may

TABLE 1 Key findings of imaging modalities in the diagnosis of the most common liver masses.

	Ultrasound	Triphasic CT	MRI
Hemangioma	Peripheral feeding vessels; low flow, hyperechoic, increased through transmission relative to normal liver	Peripheral discontinuous nodular hyperenhancement, fills in from periphery, follows blood pool enhancement on delayed phases	Peripheral discontinuous nodular hyperenhancement, fills in from periphery, follows blood pool enhancement on delayed phases, marked T2 hyperintensity (high-flow hemangiomas may show *pseudo washout*)
Focal fat	Hyperechoic, shadowing, no mass effect, no vessel displacement	Sharp interface, low attenuation (<40 HU), characteristic locations around the gallbladder fossa and falciform ligament	Diagnostic appearance on in-phase and opposed-phase imaging
FNH (<3 cm)	Homogenous isoechoic or nearly isoechoic, may be difficult to discern, occasional central hyperechoic area with centripetal flow	Lobulated, homogeneous arterial phase hyperenhancement, fades to enhancement of background liver, occasionally late enhancing central scar	Lobulated, homogeneous arterial phase hyperenhancement, fades to enhancement of background liver, occasional late enhancing central scar, isointense T2; retains gadoxetate disodium
Adenoma	Variable appearance (may be hyperechoic or hypoechoic), homogeneous or heterogeneous; demographics can be helpful	Variable appearance, may be hyperenhancing or isoenhancing, may washout or fade to enhancement of background liver, capsule, may contain fat; demographics can be helpful	Variable appearance; may be hyperenhancing or isoenhancing, may washout or fade to enhancement of background liver, capsule, may contain fat; demographics can be helpful
HCC	Hypoechoic or hyperechoic, homogeneous or heterogeneous	Arterial phase hyperenhancement, washout, capsule, often heterogeneous, may contain intratumoral vessels	Arterial phase hyperenhancement, washout, capsule, often heterogeneous, may contain intratumoral vessels
Intrahepatic cholangiocarcinoma	Hypoechoic; bile duct dilation for central tumors, no bile duct dilation for peripheral tumors	Irregular linear rim arterial phase hyperenhancement, delayed central enhancement, hepatic capsular retraction	Irregular linear rim arterial phase hyperenhancement, delayed central enhancement
Colorectal metastasis	Usually hypoechoic but can be hyperechoic, target appearance	Smooth linear rim arterial phase hyperenhancement, venous phase washout	Smooth linear rim arterial phase hyperenhancement, venous phase washout, intermediate T2w hyperintensity

Abbreviations: CT, computed tomography; FNH, focal nodular hyperplasia; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; T2w, T2-weighted. HU, Hounsfield units.

mimic the cancer, including perfusional abnormalities, hemangiomas, focal nodular hyperplasia, high-grade dysplastic nodules, small intrahepatic cholangiocarcinoma, mixed hepatocellular-cholangiocarcinoma, and, infrequently, hypervascular metastases within a cirrhotic liver (Table 1).[45,52–54]

The LI-RADS classification consists of four distinct algorithms designed to standardize terminology, reporting, and management for patients who have or are at risk for HCC (Table 2 and Figure 1).[55] This system is applied across various contexts: surveillance using US; diagnosis using CT, MRI, or contrast-enhanced US; and evaluating treatment response with CT or MRI. Adoption of this interpretive system has had a tremendous impact on the standardization of terminology and management decisions stemming directly from imaging findings. The integration of LI-RADS into the clinical setting has streamlined the communication between radiologists, oncologists, and patients by using a uniform language that enhances the accuracy of the reports and also considerably increases the consistency with which major HCC features are described in radiology reports.[56]

Role of biopsy

Although tissue biopsy is not required for diagnosing HCC in many patients, there are certain cases in which it is necessary.[57] For instance, LR-4 observations (probably but not definitely HCC) may be managed with observation or biopsy, and LR-M observations (definite malignancy, not specific for HCC) typically undergo biopsy or resection when feasible.[17] In noncirrhotic livers, in which imaging specificity for HCC decreases and LI-RADS criteria cannot be applied, a biopsy is often needed. In addition, a liver tumor biopsy is recommended for patients with suspected intrahepatic cholangiocarcinoma, mixed hepatocellular-cholangiocarcinoma, or secondary malignancies, which, in combination with histologic and serum markers, can help differentiate HCC from other tumors.[58] Another potential benefit of tissue biopsy is its ability to categorize HCC into histologic subtypes, which align with molecular classifications and carry prognostic significance. For example, it can identify highly differentiated, *CTNNB1*-mutated subtypes and poorly differentiated, *TP53*-mutated subtypes.[59–61]

TABLE 2 Liver Imaging Reporting and Data System (LI-RADS).

		No APHE		Nonrim APHE		
		<20 mm	≥20 mm	<10 mm	10–19 mm	≥20 mm
Additional major features[a]	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	°LR-4/LR-5	LR-5
	Two or more	LR-4	LR-4	LR-4	LR-5	LR-5

Abbreviations: APHE, arterial phase hyperenhancement; CT, computed tomography; HCC, hepatocellular carcinoma; LR-1, definitely benign; LR-2, probably benign; LR-3, intermediate probability of hepatocellular carcinoma; LR-4, high probability of hepatocellular carcinoma; LR-5, definitely hepatocellular carcinoma.

[a]Additional major features: enhancing "capsule," nonperipheral "washout," "threshold growth" °LR-4 if enhancing "capsule" or LR-5 if nonperipheral "washout" OR threshold growth.

With the shift toward less invasive medical techniques, liquid biopsy is a potential major advance in cancer care. This technique does not require needle placement into the tumor, thereby mitigating the risk of needle tract seeding associated with percutaneous tumor biopsies, and thus may reduce the theoretical risk of tumor dissemination and its potential impact on cancer outcomes.[62] In addition, it enables real-time, noninvasive tumor monitoring and facilitates the early detection of circulating tumor cells, cell-free DNA, noncoding RNAs, and extracellular vesicles. As biomarker-stratified trials become more common, tissue biopsies may remain essential for matching patients with optimal treatments, whereas liquid biopsies are expected to play a crucial role in early HCC detection and monitoring treatment responses, with a sensitivity ranging from 83% to 93%.[57]

STAGING SYSTEMS FOR HCC

Survival outcomes for patients with HCC have improved in recent years, which can be attributed to advances in therapeutic options, such as immunotherapy, in combination with reliable staging systems that facilitate more accurate prognostication and help the clinician personalize treatment. In the United States, the American Joint Committee on Cancer TNM system is most commonly used and assesses tumor size (T), lymph node involvement (N), and distant metastasis (M).[63] Although the TNM system provides a detailed assessment of the extent of liver cancer, it does not account for liver function. To address this limitation, other staging systems have been developed that incorporate both tumor characteristics and liver function. Notable among these are the Barcelona Clinic Liver Cancer (BCLC) system (the most widely used), the Cancer of the Liver Italian Program score, and the Okuda system.[64–66] Each of these staging systems is summarized in Table 3.

The BCLC system is frequently used alongside the TNM system[17,67,68] and was developed based on findings from multiple cohort studies and randomized controlled trials (RCTs) conducted by the Barcelona group. Although the BCLC staging system was originally developed for the stratification and treatment allocation of patients with cirrhosis and HCC, it is also commonly applied to patients without cirrhosis. The BCLC staging system incorporates tumor size, the presence of metastatic disease, portal hypertension, the CTP score, the total bilirubin level, and performance status and has distinct algorithms to direct treatment[65] (Table 3 and Figures 2 and 3). Common critiques of the BCLC system, however, include the lack of consideration of tumor behavior and disease heterogeneity as well as its historically restrictive nature pertaining to BCLC-B patients who may benefit from surgical management.

In 2022, an updated BCLC classification was published[65] that not only addresses these known shortcomings in the older classification system but also encompasses modern-day therapeutic advances. First, the 2022 guidelines support individualized care based not only on patient and disease characteristics but also on local expertise and technical availability. Second, the update recognizes LT as a key objective. Unlike the 2018 version, in which LT was recommended only for multifocal HCCs ≤3 cm, the 2022 guidelines include three pathways to LT: small multifocal HCCs, a subgroup patients with BCLC stage B HCC, and patients successfully downstaged with transarterial chemoembolization (TACE) or transarterial radioembolization (TARE). The 2022 BCLC classification further stratifies patients with BCLC stage B HCC into three subgroups based on tumor burden and liver function and suggests the appropriateness of some treatment strategies as well as the futility of others. The first subgroup includes patients who are candidates for LT if they meet the *extended LT criteria* (typically based on tumor size and/or AFP levels), as defined by each institution or country. The second subgroup consists of patients who are not eligible for LT but have preserved portal flow and well defined, arterially fed nodules, supporting selective transarterial therapy. The third subgroup comprises patients with diffuse, infiltrative, or extensive bilobar liver involvement, for whom systemic therapy is recommended because they are unlikely to benefit from transarterial therapy.

Although the BCLC system remains the most widely adopted, recommendations for surgical management in patients with early stage HCC remain conservative. Specifically, surgical resection is only recommended for patients who have BCLC stage 0 or A with solitary tumors despite data supporting consideration of surgical resection among patients with multinodular HCC, especially BCLC stage A tumors (three or fewer nodules, each ≤3 cm).[69–72]

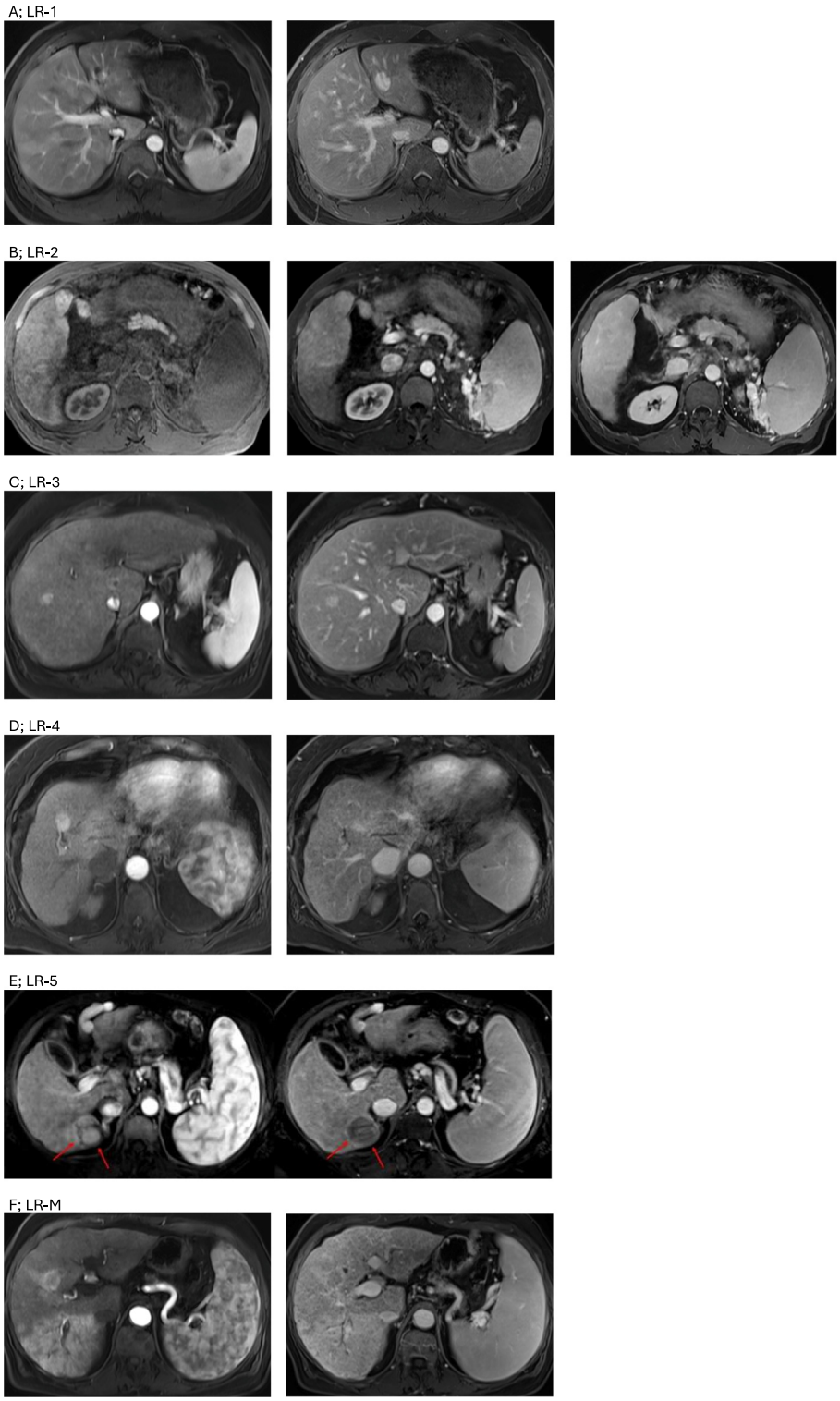

FIGURE 1 Imaging characteristics of LI-RADS lesions and the associated risk of HCC. (A) LR-1: 2.2-cm observation with peripheral nodule enhancement and gradual fill-in; definitely benign. (B) LR-2: 2.9-cm, distinct, T1-hyperintense observation with no arterial phase hyperenhancement, washout, or capsule. Approximately 16% of LR-2 lesions are HCC, and 18% are malignant (C) LR-3: 1.3-cm observation with nonrim arterial phase hyperenhancement, no washout or capsule, and faint, persistent enhancement in the delayed phase. Approximately 37% of LR-3 lesions are HCC, and 39% are malignant. (D) LR-4: 2.1-cm observation with nonrim arterial phase hyperenhancement and no washout or capsule. Approximately 74% of LR-4 lesions are HCC, and 81% are malignant. (E) LR-5: 4.4-cm mass in the medial aspect of segment 6 with heterogeneous mass-like arterial phase hyperenhancement, washout, and capsule. Approximately 95% of LR-5 lesions are HCC, and 98% are malignant. (F) LR-M: 2.4-cm observation with rim arterial phase hyperenhancement, questionable washout, and no capsule. DEB-TACE indicates drug-eluting bead transarterial chemoembolization; HCC, hepatocellular carcinoma; LI-RADS, Liver Imaging Reporting and Data System; TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization.

TABLE 3 Staging systems for hepatocellular carcinoma.

Tumor-node-metastasis (TNM) classification

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Solitary tumor ≤2 cm, or >2 cm without vascular invasion
T1a	Solitary tumor ≤2 cm
T1b	Solitary tumor >2 cm without vascular invasion
T2	Solitary tumor >2 cm with vascular invasion, or multiple tumors, none >5 cm
T3	Multiple tumors, at least one of which is >5 cm
T4	Single tumor or multiple tumors of any size involving a major branch of the portal vein or hepatic vein, or tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of visceral peritoneum
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

TNM staging groups

Stage	T	N	M
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
IVA	Any T	N1	M0
IVB	Any T	Any N	M1

Barcelona Clinic Liver Cancer (BCLC) prognostic groups

Stage	Definition (tumor features, liver function, performance status [PS])	Treatment
Very early stage (0)	• Single ≤2 cm • Preserved liver function • PS 0	• Resection • If portal hypertension/hyperbilirubinemia, transplantation is recommended • If other clinical comorbidities, radiofrequency ablation is then recommended
Early stage (A)	• Single, or three or fewer nodules each ≤3 cm • Preserved liver function • PS 0	• Resection is viable for single lesions • If multiple lesions, transplantation is recommended • If other clinical comorbidities are present, radiofrequency ablation is recommended
Intermediate stage (B)	• Multinodular • Preserved liver function • PS 0	• Management is usually recommended to be transcatheter arterial chemoembolization
Advanced stage (C)	• Portal invasion and/or extrahepatic spread • Preserved liver function • PS 1–2	• Management is usually palliative or clinical trials

TABLE 3 (Continued)

Barcelona Clinic Liver Cancer (BCLC) prognostic groups		
Stage	**Definition (tumor features, liver function, performance status [PS])**	**Treatment**
Terminal stage (D)	• Any tumor burden • End-stage liver function • PS 3–4	• Symptomatic treatment only

Histologic grade (G)	
GX	Grade cannot be accessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Fibrosis score	
F0	Fibrosis score 0–4 (none to moderate fibrosis)
F1	Fibrosis score 5–6 (severe fibrosis or cirrhosis)

Cancer of the Liver Italian Program (CLIP) score				
Child–Pugh stage	A	B	C	
Tumor morphology	Uninodular and extent ≤50% of liver	Multinodular and extent ≤50% of liver	Massive or extent >50% of liver	
α-Fetoprotein, ng/mL	<400		≥400	
Portal vein thrombosis	No		Yes	
Score	0	1	2	3

Okuda staging	
Factors • Disease involving >50% of hepatic parenchyma • Ascites • Albumin ≤3 mg/dL • Bilirubin ≥3 mg/dL	
Stage I	No factors present
Stage II	One or two factors present
Stage III	Three or four factors present

GENERAL THERAPEUTIC APPROACH

Although clinicians rely on staging systems like the BCLC classification to inform prognosis and treatment, HCC remains a heterogenous disease in a patient population with variable hepatic function and physical performance status. Therefore, patients ideally should be managed within a multidisciplinary team to personalize treatments that achieve the most favorable outcomes.[73] In this section we detail specific treatment strategies and the data supporting their use, guided by the therapeutic algorithm in Figure 3. The wide variety of treatments for HCC are delivered by different specialties: surgery, interventional radiology, radiation oncology, medical oncology, and transplant hepatology. Thus the suggested approach is useful for conceptualizing the various treatment options that may be applied for individual patients dictated by extent of disease (early stage vs. locally advanced vs. systemic disease), hepatic function, and performance status. In addition, for reference, a selection of ongoing clinical trials in progress is summarized in Table S1.

EARLY STAGE HCC: SOLITARY TUMORS AND MULTIFOCAL DISEASE WITHIN TRANSPLANTATION CRITERIA

Surgical treatment, including partial hepatectomy and LT, offers long-term survival with a good quality of life and is one of the only potentially curative treatments for HCC (Figures 2 and 3). Patients

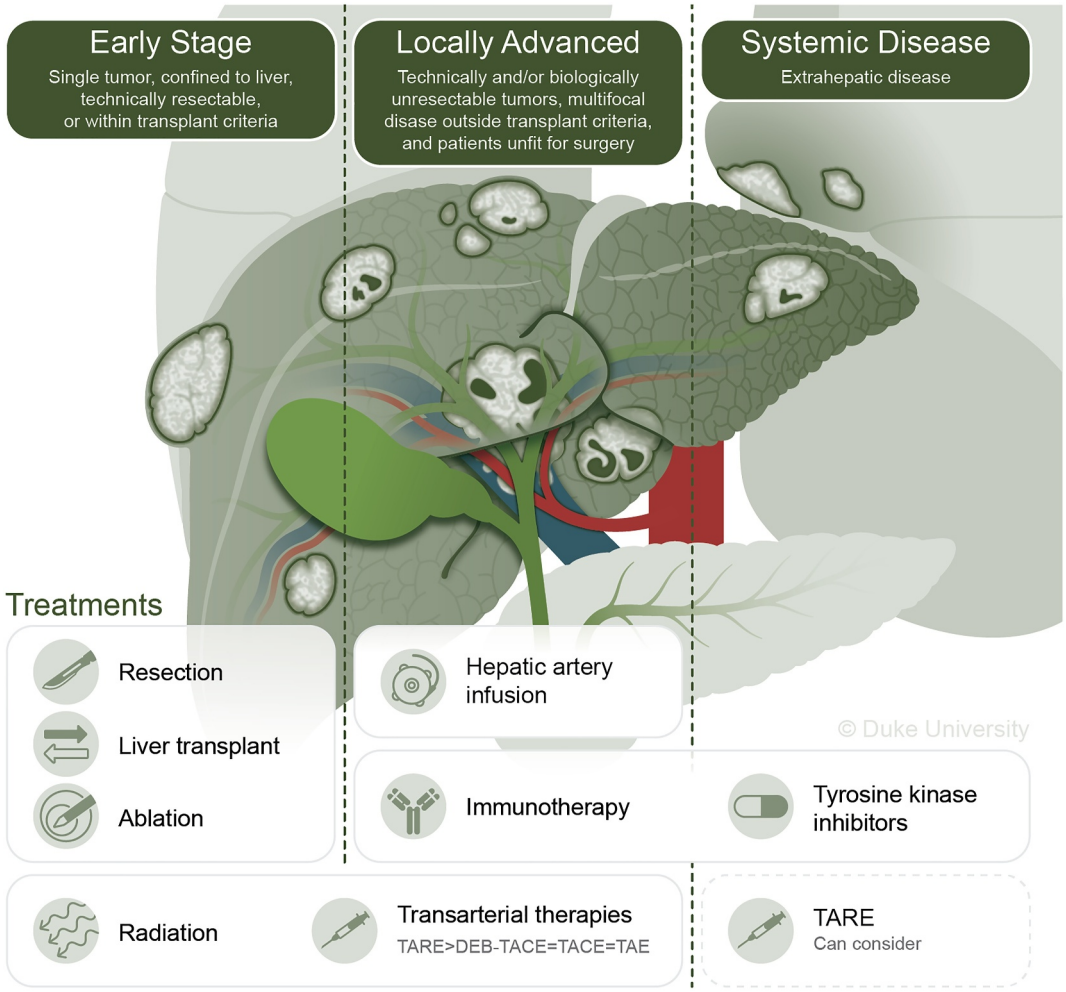

FIGURE 2 Emerging treatment strategies for the management of HCC. Early stage HCC, defined as a single tumor confined to the liver that is technically resectable and/or within transplantation criteria, is most effectively managed with local therapies, such as partial hepatectomy, liver transplantation, ablation, radiation, or transarterial therapies. Locally advanced HCC, including technically and/or biologically unresectable tumors, multifocal disease outside of transplantation criteria, or patients unfit for surgery, is most effectively managed with transarterial therapies with or without systemic therapy. Systemic disease, which includes distant metastatic HCC, relies on systemic therapy as the cornerstone of treatment. DEB-TACE indicates drug-eluting bead transarterial chemoembolization; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization.

ideally suited for liver resection have localized HCC confined to the liver without radiographic evidence of invasion of the liver vasculature, preserved hepatic function, and no evidence of portal hypertension (although a minor resection could be considered in some patients who have portal hypertension).[74,75] Although LT theoretically offers a better chance of cure over resection,[76–78] several factors, including organ availability, limit its widespread use; thus liver resection remains the standard therapy for most patients who have resectable HCC.[79]

Partial hepatectomy

Generally, liver resection is the treatment of choice among patients without cirrhosis. Unfortunately, less than one half of patients who are considered for hepatectomy are indeed resectable based on several patient-specific and disease-specific factors (Table 4).[80,81] In noncirrhotic patients as well as those who have compensated cirrhosis, resection is recommended if HCC presents as a single tumor, regardless of size, assuming the patient has adequate liver remnant volume and preserved liver function (CTP class A with total bilirubin <1.5 mg/dL; Model for End-Stage Liver Disease [MELD] score, <9) without clinically significant portal hypertension, and a good performance status.

Anatomic resection has been associated with improved recurrence-free survival (RFS) and overall survival (OS) compared with nonanatomic resection; however, nonanatomic resection is often appropriate to preserve parenchyma and mitigate the risk of postoperative hepatic insufficiency.[82,83] There is currently a lack of strong evidence to support a clear magnitude of negative margin to be achieved during resection of HCC. Most observations come from retrospective studies, from which the conclusions may be affected by

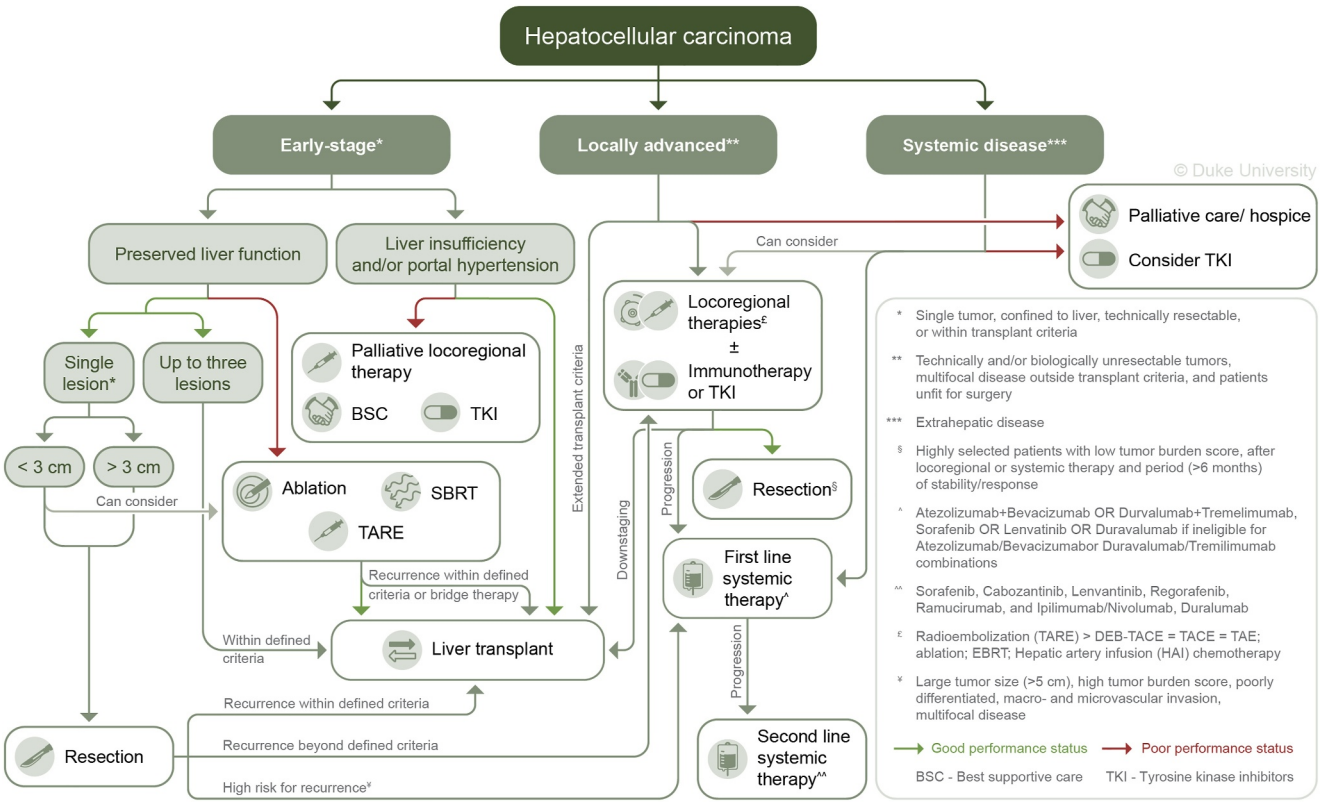

FIGURE 3 The Proposed Duke Clinic treatment algorithm for the management of HCC based on patient-specific and disease-specific characteristics. Note that treatment algorithms vary depending on the patient's performance status. EBRT indicates external-beam radiation; DEB-TACE drug-eluting bead transarterial chemoembolization; HCC, hepatocellular carcinoma; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization.

TABLE 4 Key considerations in determining resectability (suitability for partial hepatectomy) of hepatocellular carcinoma.

Category	Resectable	Unresectable
Performance status	ECOG performance status of 0–1	ECOG performance status ≥2
Liver function/cirrhosis	Compensated cirrhosis (Child–Pugh A-B7, with total bilirubin<1.5 mg/dL; MELD <9)	Decompensated cirrhosis (Child–Pugh B8-C)
Portal hypertension	Absent: HVPG <10 mmHg generally indicates lower perioperative risk	Present: Significant portal hypertension (HVPG ≥10 mmHg) or clinically manifested by splenomegaly, esophageal varices, recanalized umbilical vein, and/or thrombocytopenia
Single vs. multifocal disease	Single	Multifocal
Extrahepatic disease	Absent	Present
Large vessel invasion	Absent	Present
Technical ability to achieve negative margins	Margin-negative resection can be achieved with preservation of an adequate liver remnant with sufficient inflow/outflow/biliary drainage	Margin-negative resection that would require resection of all three hepatic veins, both portal veins and the retrohepatic vena cava, and/or would leave an inadequate liver remnant
Future liver remnant	Adequate: Noncirrhotic, >30%; cirrhotic, >40% to 50%	Inadequate: Noncirrhotic, <30%; cirrhotic, <40% to 50%

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HVPG, hepatic venous pressure gradient; MELD, Model for End-Stage Liver Disease.

selection bias. The only RCTs available to date report a benefit in terms of local control within 2 years from surgery for wide anatomic margins (up to 2 cm) in patients who have a single HCC with preserved liver function.[84–86]

Because of recent advances in surgical techniques and perioperative care, postoperative mortality after HCC resection among patients with cirrhosis is now <5%, yet postoperative liver decompensation still ranges from 10% to 12%.[87] Predictors of liver

decompensation include the extent of liver resection, fibrosis, the presence of portal hypertension, and a MELD score >9 or 10.[88–90] In patients with cirrhosis and portal hypertension, resection should be considered on an individual basis, carefully weighing risks versus benefits and considering alternative treatment strategies (e.g., embolotherapies) because even a minor hepatectomy in this population can result in postoperative hepatic insufficiency and death.[17,91,92] A large retrospective study evaluating the role of liver resection in patients with HCC and clinically significant portal hypertension was just completed (ClinicalTrials.gov identifier NCT06245798) and is anticipated to clarify the role of surgery for this population.

Although current guidelines reserve partial hepatectomy for patients who have solitary tumors without macrovascular invasion and sufficient hepatic functional reserve, accumulating evidence suggests that it may be a reasonable option for highly selected patients who have multifocal (up to three tumors) HCC and/or macroscopic vascular invasion because they may achieve a survival benefit from surgery compared with TACE, systemic therapy, or radiation alone.[93–98] This advantage is clearer in patients who have three or fewer tumors.[99] No study has identified a cutoff value of the number of HCC foci beyond which resection is contraindicated. The limit of three nodules has been fixed in analogy with Milan criteria. Even if it is reasonable, results of surgery beyond this threshold are lacking. Also, there is ongoing debate about the definition of multifocal HCC because often it is a misclassification of satellite nodules (macroscopic or microscopic tumor foci situated close to the main tumor [≤20 mm] into the same segment, probably caused by HCC microscopic vascular invasion). Moreover, the distinction between multicentric and metastatic HCC deserves more attention: multicentric disease is the occurrence of multiple synchronous HCCs, while metastatic disease is the onset of a primary tumor with rapid development of intrahepatic metastases. Despite all of these limitations, these historical boundaries have been challenged. In 2008, Ishizawa et al. reported the first large retrospective series with favorable results for 126 patients who underwent resection of multifocal disease, which was associated with a 5-year survival rate of 58%, although multivariable analysis revealed that the presence of multiple tumors was an independent risk factor for recurrence (hazard ratio [HR], 1.64).[95] In 2013, Torzilli et al. analyzed more than 2000 patients undergoing liver resection for HCC worldwide, including 333 with multiple HCCs.[96] Patients with BCLC stage B disease (including both large and multinodular HCCs) achieved a 57% 5-year survival rate. Recently, Fukami et al. analyzed the Japanese nationwide registry, in which 1944 patients who had two or three HCCs underwent surgery were compared with 1302 patients who had a similar tumor burden and underwent chemoembolization.[97] Patients in the resection group had better survival both in the whole series (5-year survival, 59% vs. 42%; $p < .001$) and after propensity score matching (60% vs. 42%; $p < .001$), independent of HCC size (≤30 or >30 mm). A recent retrospective study of 5000 patients with multinodular HCC, after a matching-adjusted, indirect comparison, demonstrated that resection produced 1-year, 3-year, and 5-year survival rates of 89.1%, 70.9%, and 56.4%, respectively, compared with radiofrequency ablation (RFA), which produced rates of 94.0%, 65.2%, and 39.9%, respectively, while TACE produced respective rates of 90.9%, 48.9%, and 29.2%.[98] Multivariable Cox survival analysis in the weighted population demonstrated a survival benefit in patients undergoing resection over alternative treatments (RFA vs. liver resection: HR, 1.41; 95% confidence interval [CI], 1.07–1.86; $p = .01$; TACE vs. liver resection: HR, 1.86; 95% CI, 1.29–2.68; $p = .001$).[98]

The role of surgery versus chemoembolization in patients with BCLC stage B HCC is further supported by a retrospective study across multiple institutions[100] and one randomized trial.[72] The RCT from China included 2502 patients who had HCC over a 22-month period (from November 2008 to September 2010), including 173 patients who had multinodular HCC beyond Milan criteria, and demonstrated that liver resection improved survival compared with TACE (1-year, 2-year, and 3-year OS: 76.1%, 63.5%, and 51.5% vs. 51.8%, 34.8%, 18.1%; $p < .001$). The same difference persisted in patients who had more than three nodules, but only 11 of such patients were included. Multivariate Cox proportional hazards regression analysis revealed that surgical resection (HR, 0.434; 95% CI, 0.293–0.644; $p < .001$), the number of tumors (HR, 1.758; 95% CI, 1.213–2.548; $p = .003$) and sex (HR, 0.451; 95% CI, 0.236–0.862; $p = .016$) were independent risk factors associated with OS. One limitation of this study is the relatively lower survival rates in the TACE group compared with those reported in contemporary studies.[101–104] Specifically, TACE with drug-eluting beads (DEB-TACE) has been associated with better survival outcomes compared with conventional TACE (cTACE); however, this treatment option was not available in China at the time of the trial.[105] It should be clear that the decision to recommend hepatectomy for patients with multifocal HCC is highly nuanced, thus patients selected for this approach should be evaluated in a multidisciplinary setting.

Liver transplantation

Patients with chronic liver disease and HCC are considered to have a field defect, in which cancer can develop anywhere in the liver. Therefore, LT for HCC is a conceptually attractive treatment strategy because it allows for complete removal of the cancer with negative margins while simultaneously replacing the diseased liver, which otherwise would remain at risk for the development of additional HCC tumors. Transplantation is particularly relevant for patients with HCC in the setting of liver dysfunction, advanced cirrhosis, and/or portal hypertension.

The Milan criteria (Table 5), which requires patients to have a solitary HCC up to 5 cm in greatest dimension or up to three tumors, none of which can be greater than 3 cm, and no macrovascular invasion, nodal metastases, or distant metastases, were first published in 1996 and have since been accepted worldwide and incorporated into the United Network for Organ Sharing criteria as an approved indication for LT and to determine priority listing status.[106] These

TABLE 5 Eligibility criteria for liver transplantation and prognostic scores.

Transplantation criteria	
Milan criteria	Single nodule ≤5 cm, up to three lesions ≤3 cm each, without vascular invasion, nodal involvement, and without extrahepatic metastases
UCSF criteria	Single lesion <6.5 cm, or three or less lesions <4.5 cm each, with a total greatest tumor dimension <8 cm
Metroticket	Maximum size of the tumor, number of tumor nodules, and presence/absence of microvascular invasion + AFP
UNOS criteria	AFP ≤100 ng/mL, tumor 2–5 cm in greatest dimension or two or three tumors 1–3 cm in greatest dimension, no macrovascular involvement, no extrahepatic disease
Up to 7 criteria	Sum of the size of the largest tumor (in cm) and number of tumors seven or fewer, absence of microvascular invasion
AFP French model	Point system based on tumor size, number, and AFP levels
Prognostic scores	
RETREAT score	AFP recent, microvascular invasion, and a composite score of largest viable tumor dimension and number of viable tumors
TBS	$TBS^2 = (\text{maximum tumor diameter})^2 + (\text{number of tumors})^2$
UCLA Nomogram	Nuclear grade, degree of vascular invasion, pre-LT beyond MC and not downstaged, radiologic maximum tumor dimension >5 cm if nonincidental, NLR, AFP max, and total cholesterol
HALTHCC	MELD-Na, TBS, AFP, year of transplantation, underlying cause of cirrhosis, neutrophil-lymphocyte ratio, history of locoregional therapy, and Milan criteria status
MORAL score	NLR >5, AFP max >200, maximum tumor dimension >3 cm, tumor number greater than three, vascular invasion, and grade 4 tumors
RELAPSE score	0.389 * log NLR + 0.354 * log Max AFP + 2.21 * (log pathologic max diameter +1) + 0.560 (if moderate grade) + 0.816 (if poor grade) −0.265 (if necrotic) + 0.861 (if microvascular invasion) + 1.218 (if macrovascular invasion)

Abbreviations: AFP, α-fetoprotein; HALTHCC, Hazard Associated with Liver Transplantation for Hepatocellular Carcinoma; LT liver transplantation; max, maximum; MC, Milan criteria; MELD, Model for End-Stage Liver Disease; MORAL, model of recurrence after liver transplantation; NLR, neutrophil-lymphocyte ratio; RELAPSE, Recurrent Liver Cancer Prediction Score; RETREAT, Risk Estimation of Tumor Recurrence After Transplant; TBS, transplant benefit score; UCLA, University of California-Los Angeles; UCSF, University of California-San Francisco; UNOS, United Network for Organ Sharing.

criteria have revolutionized patient selection for LT and have aided in overcoming the historically poor outcomes after transplantation for HCC compared with nonmalignant indications, including high 90-day mortality rates, recurrence rates up to 80%, and poor long-term survival, all of which plagued early experience with transplantation for HCC.[107,108] Consequently, from an oncologic standpoint, LT is now considered to provide the best long-term outcomes for patients who present with transplantable HCC, with 5-year survival exceeding 70% and recurrence rates less than 10%–15%.[109] The main criticism of the Milan criteria is that they result in a dichotomous score that is perhaps too restrictive, incapable of discerning disease heterogeneity, and thus commonly excludes patients with HCC outside of Milan criteria who might actually benefit from LT. Therefore, in recent years, several other criteria for LT have been proposed to expand eligibility for LT (Table 5). The University of California-San Francisco criteria are the most widely applied extended criteria for LT in HCC and have been validated.[110] Indeed, use of University of California-San Francisco criteria might expand the pool of candidates for LT by up to 20%.[111] For completeness, Table 5 lists other current eligibility criteria for LT, including the United Network for Organ Sharing criteria, up to seven criteria, the Metroticket score, and the AFP French model. Table 5 also includes post-LT prognostic outcome scores; however, these are not applicable during the patient-selection phase.

Because of the necessary waiting time after transplant candidacy is approved, including meeting Milan or other criteria for HCC burden, patients are at risk of HCC progression outside of criteria and losing transplant candidacy. *Bridging* therapy entails the use of locoregional therapies to control or eradicate any HCC during the mandatory waiting period and while awaiting organ availability to maximize chances that the patient will remain within criteria until an organ is available. Although various liver-directed therapies have been used, an analysis of 3601 patients from the US Multicenter HCC Transplant Consortium revealed that a complete histopathologic response was correlated with significantly greater RFS versus patients who were untreated or who had only a partial response. In fact, patients who had a partial response had a higher recurrence rate than those who were untreated.[112] In a single-institution study on

transplanted patients who underwent bridge therapy, the pathologic complete response rate in explanted livers was 28.5% after stereotactic body radiotherapy (SBRT), 41% after TACE, 60% after RFA, and 75% after radioembolization.[113]

Another method to expand eligibility for LT is the concept of downstaging patients outside of transplant criteria using locoregional therapies to decrease disease burden and to meet Milan or extended criteria (Figure 3). Reported success rates in downstaging HCC vary widely from 24% to 90%, likely influenced by the chosen downstaging treatment, initial tumor burden, and tumor biology.[114] After successful downstaging to transplantable disease, transplant recipients can achieve excellent posttransplant outcomes and low recurrence rates that mimic the outcomes of patients who initially were within criteria. In a randomized trial, patients with HCC beyond Milan criteria who were downstaged (with chemoembolization, RFA, radioembolization, or resection) had a 5-year posttransplantation OS rate of 77.5%.[114] Therefore, the 2022 BCLC guideline updates have now included LT as an acceptable treatment approach for individuals who have BCLC stage B HCC after downstaging of their HCC to within Milan criteria.[65] Exploring the role of ICIs in downstaging is crucial because they have significantly improved the management of intermediate-stage and advanced-stage HCC, potentially making some patients eligible for LT.[115] However, long-term survival and recurrence outcomes have not yet been reported. Neoadjuvant ICIs may benefit select LT candidates, but ongoing challenges include understanding response indicators and managing post-LT risks, including rejection.[116]

Another important consideration in LT as a management strategy for HCC is organ availability, especially in countries with an opt-in donation system, such as the United States. Currently, patients who have HCC within Milan criteria receive priority on the LT waiting list and compete with patients who do not have HCC.[117] This current allocation system appears advantageous to patients with HCC because of fewer patients *falling off* of transplantation waiting lists, regardless of geography.[117] Alternatively, living donation negates wait time and the risk of dropout from eligibility, although it raises the ethical question of whether it is justifiable to subject a healthy donor to the risks of major hepatectomy for donation, especially if the recipient has a reasonable chance of receiving an organ from a donor who has died. Studies comparing the outcomes of patients with HCC after a living donor LT (LDLT) and a deceased donor LT (DDLT) suggest that an LDLT is associated with improved outcomes. An intention-to-treat analysis produced 1-year, 3-year, and 5-year OS rates that were significantly better in the LDLT group compared with the DDLT group (94.1% vs. 77.5%, 81.4% vs. 48.7%, and 75.9% vs. 40.8%, respectively).[118] Disease recurrence and recipient complications are similar with LDLTs, whereas dropout is lower because patients are not required to be waitlisted. Thus an LDLT should be considered in the setting of refined inclusion criteria and optimized tumor management.[119]

Given graft scarcity in many countries, even for patients within LT criteria, it is important to understand how LT outcomes compare with the outcomes associated with partial hepatectomy for HCC management. A recent meta-analysis comparing LT versus resection in patients who were eligible for both treatment modalities demonstrated that LT was superior to resection in terms of 5-year OS and RFS in all patients with HCC (OS: odds ratio [OR], 0.79; 95% CI, 0.67–0.93; level of heterogeneity [I^2], 57%; RFS: OR, 0.44; 95% CI, 0.25–0.75; I^2, 96%). Salvage LT (LT for recurrence after liver resection) versus primary LT did not differ between 5-year OS and RFS (OS: OR, 0.62; 95% CI, 0.33–1.15; I^2, 0%; RFS: OR, 0.93; 95% CI, 0.82–1.04; I^2, 0%).[120] The survival benefit is most profound in patients who have multifocal disease within Milan criteria (specifically, a greatest tumor dimension <3 cm without major vascular invasion), with a HR of 0.39 (95% CI, 0.30–0.50) relative to resection.[121] Although LT appears to be associated with improved outcomes compared with resection, organ availability continues to limit access to this therapy for many patients; thus patients with technically and biologically resectable HCC who have good performance status and normal hepatic function without portal hypertension should be prioritized for resection.

Adjuvant therapy in patients undergoing surgery with curative intent

Adjuvant therapy is not offered as a standard-of-care option, even for patients who remain at high risk for HCC recurrence after curative-intent resection or ablation, although the incidence of recurrence may be as high as 88%.[122,123] This remains an area of high unmet need because no beneficial therapies have been reported. Sorafenib, a tyrosine kinase inhibitor (TKI), which, until recently, was the first-line treatment for advanced HCC,[18] was explored as an adjuvant therapy in the STORM trial (ClinicalTrials.gov identifier NCT00692770). This large RCT, which that included 1114 patients (80% undergoing curative-intent resection), reported no significant difference in median RFS compared with placebo (33.3 months in the sorafenib group vs. 33.7 months in the placebo group; HR, 0.940; 95% CI, 0.780–1.134; one-sided, $p = .26$).[124]

The phase 3 IMbrave050 trial (ClinicalTrials.gov identifier NCT04102098) randomly assigned (1:1) high-risk patients to receive adjuvant atezolizumab (1200 mg) plus bevacizumab (15 mg/kg) every 3 weeks for 17 cycles (12 months) or active surveillance. Although the initial analysis of RFS suggested an improvement with adjuvant atezolizumab/bevacizumab, updated efficacy data presented at the European Society for Medical Oncology Congress 2024 suggested otherwise. RFS with atezolizumab/bevacizumab was 33.2 months versus 36 months with active surveillance (HR, 0.90; 95% CI, 0.72–1.12). Furthermore, while OS data remain immature, there was no improvement with adjuvant atezolizumab/bevacizumab (HR, 1.26; 95% CI, 0.85–1.87). Despite an acceptable safety profile, these data do not support the routine use of this adjuvant regimen for patients with high-risk HCC who undergo hepatectomy or ablation.[125]

Adjuvant locoregional therapies have also been investigated in several RCTs, suggesting a potential role for TACE or radiation after curative-intent surgery.[126,127] However, further studies are required to define the role of such strategies, as they are not considered

standard of care at this time. Similarly, several pharmacologic clinical trials—such as CheckMate 9DX, EMERALD-2, and Keynote-937 (ClinicalTrials.gov identifiers NCT03383458, NCT03847428, and NCT03867084, respectively)—are still ongoing and may provide additional insights once results become available.[128–130]

LOCALLY ADVANCED HCC: TECHNICALLY AND/OR BIOLOGICALLY UNRESECTABLE TUMORS, MULTIFOCAL DISEASE OUTSIDE TRANSPLANTATION CRITERIA, AND PATIENTS NOT CANDIDATES FOR SURGERY

Locoregional therapies—used as stand-alone treatments or in conjunction with systemic therapies—have emerged as important tools to control HCC in various circumstances. Liver-directed therapy in the form of transarterial therapies, ablation, and radiation are considered on the basis of patient (performance status, liver function), tumor-specific (extent of disease within the liver and relation with intrahepatic and gastrointestinal luminal structures), and institutional (practice patterns, available expertise) factors. As noted above, optimal therapy is best ascertained by a multidisciplinary team, considering the nuanced factors that determine the risks and benefits of each type of therapy for a given patient and tumor. Each of the commonly deployed treatment modalities are reviewed below as they pertain to locally advanced disease, but it should be noted that locoregional therapy is also commonly deployed for early stage HCC with curative intent (Figures 2 and 3).

TRANSARTERIAL THERAPIES

It is well established that liver tumors, including HCC, derive their blood supply predominantly from branches of the hepatic artery, whereas normal liver parenchyma has a dual blood supply, with the minority derived from the hepatic arterial circulation and the majority from the portal venous circulation. Transarterial therapies exploit this inherent differential to achieve significantly higher delivery of particles and/or chemotherapy/radiotherapy directly to tumors than to normal parenchyma, which results in a selective tumor therapeutic effect with relative sparing of normal parenchyma and negligible systemic toxicity. Such therapies have become a cornerstone of the treatment for locally advanced, inoperable HCC, with increasing data supporting their use in early stage HCC as well.

Transarterial embolization and TACE

Transarterial embolization (TAE), also referred to as bland embolization, constitutes the targeted introduction of embolic materials—such as polyvinyl alcohol, gelfoam, and acrylic copolymer gelatin particles—into the arterial supply of neoplastic tissue with the goal of inducing tumoral ischemia and necrosis.[131] After delineating the arterial supply of one or more tumors, the embolic is infused typically until stasis of flow is achieved. Contrast-enhanced CT or MRI is then used to assess the treatment response, with expectation of tumoral necrosis and regression. Hepatic ischemia is extremely rare unless portal venous occlusion is also present, which is generally a contraindication to TAE. Postembolization syndrome, consisting of transient right upper quadrant or epigastric pain, fatigue, anorexia, low-grade fever, and mild leukocytosis, occurs in the majority of treated patients.

TACE entails the addition of one or more chemotherapeutic agents to an embolic agent. By doing so, the local concentration of chemotherapeutic agents in tumor is markedly increased compared with that in normal parenchyma and systemically, and the embolic effect allows prolonged retention within the tumor. cTACE involves mixing a chemotherapeutic agent, such as cisplatin or doxorubicin, with gelatin sponge or lipiodol, which is a radiopaque oil that has an embolic effect. The mixture is then infused into the hepatic arterial supply of a tumor. Randomized clinical trials comparing TACE versus supportive therapy demonstrated significantly improved survival with TACE, establishing it as the standard of care for unresectable, locally advanced HCC for almost 2 decades.[101,132]

DEB-TACE subsequently emerged as an innovative drug-delivery modality to simplify the delivery of chemotherapeutic.[133] These specially designed microspheres take up a chemotherapeutic agent and releases it slowly over time. The PRECISION V trial (ClinicalTrials.gov identifier NCT00261378) was a prospective study that randomized 212 patients with advanced HCC to receive either doxorubicin-based DEB-TACE versus cTACE. In this study, DEB-TACE elicited higher rates of complete response, objective response, and disease control but was not superior to TACE when considering the primary end point of tumor response at 6 months ($p = .11$).[134] In a randomized trial by Golfieri et al., 177 patients received either cTACE or DEB-TACE. Adverse events were similar across both groups, with the notable exception of postprocedural pain, which was more frequent and severe in the cTACE group ($p < .001$). Survival rates at 1 year and 2 years indicated no significant difference, standing at 86.2% and 56.8%, respectively, for DEB-TACE and at 83.5% and 55.4%, respectively, for cTACE ($p = .949$).[135] The uncertainty regarding the efficacy and safety results has been reassessed through a meta-analysis of the randomized trials that favored DEB-TACE over cTACE.[136,137] DEB-TACE demonstrated an increased complete response rate (OR, 1.38; 95% CI, 1.01–1.89), an improved OS rate (OR, 1.41; 95% CI, 1.01–1.98), and an extended survival time (weighted mean difference, 6.65; 95% CI, 6.15–7.14), alongside fewer adverse events (OR, 0.59; 95% CI, 0.41–0.84). However, both treatments hade comparable rates of serious adverse events (OR, 0.86; 95% CI, 0.50–1.49).

Theoretically, the addition of chemotherapeutic may allow increased local cytotoxicity given its high concentration in tumors; however, whether the addition of chemotherapeutic agents to embolic agents improves tumoral response continues to be a controversial topic. Indeed, various randomized clinical trials conducted from the 1980s to the early 2000s yielded inconsistent

results.[101,131,132,138–141] A meta-analysis and subsequent reviews, which examined randomized clinical trials comparing survival outcomes following TAE and TACE, found no significant differences in survival rates between bland and chemoembolization.[142,143] These findings suggest that the ischemia and necrosis induced by the embolization process itself may play a more crucial role than the effects of the chemotherapy. In a contemporary randomized clinical trial, Brown et al. observed no significant differences comparing the outcomes of embolization using microspheres alone to those of chemoembolization with doxorubicin-eluting microspheres.[144]

Transarterial radioembolization

TARE uses the β-emitter yttrium-90, which is selectively delivered to the tumor's arterial vasculature using resin or glass microspheres, thereby achieving a targeted tumoricidal effect.[145] Although it is a particle-based transarterial therapy, the number and size of particles are grossly inadequate to produce a significant embolic effect (stasis is not achieved), thus the mechanism of action is cellular irradiation without significant ischemia. TARE has several clinical utilities, including tumor downsizing,[146] bridging to LT,[147] controlling tumor burden while inducing hypertrophy of the future liver remnant before resection (radiation lobectomy),[147,148] providing palliation or delaying disease progression in advanced HCC, and serving as a primary curative treatment modality for isolated liver lesions.[149,150] Radioembolization is also the only transarterial therapy with efficacy and safety for treating vascular invasion, including the potential for complete histopathologic responses.[151,152]

The prescribed dose of yttrium-90 can vary drastically (often between 50 and 500 gray [Gy]) based on tumor, liver, and patient factors, because its effects on the targeted tumor and normal parenchyma are dose-dependent, as with all radiation-based therapies.[153] It is notable that early trials were all performed using standardized dosing strategies, in which modest doses were administered to large volumes of liver, whereas modern principles entail delivering high doses to the smallest amount of parenchyma possible. High tumor-absorbed doses correlate with high degrees of tumoral necrosis. However, higher levels of parenchyma-absorbed doses correlate with greater degrees of radioembolization-induced liver disease and worsening of hepatic fibrosis. Thus the strategy of maximum dose to minimal parenchyma is preferred. It has been hypothesized that this evolution in strategic dosimetry is a reason for disparate results comparing prior randomized clinical trials investigating TARE for HCC using conventional dosimetry versus more current trials using personalized dosimetry. To address this question, the DOSISPHERE-01 RCT (ClinicalTrials.gov identifier NCT02580234) investigated the difference between standard dosimetry TARE with 120 Gy delivered to the treated hepatic lobe versus personalized dosimetry with at least 205 Gy delivered to the target lesion.[154] In this French phase 2 study, which included 60 patients who had at least one lesion ≥7 cm, of whom 68% had portal vein invasion, those who received treatment with personalized dosimetry had an objective response rate of 71% versus only 36% with standard dosing ($p = .0074$).[154] At least one adverse event was observed in 20% of the patients who received personalized dosimetry and 33% of those who received standard dosimetry, including ascites (3% vs. 10%), hepatic failure (6% vs. none), lymphopenia (35% vs. 43%), gastrointestinal hemorrhage (none vs. 10%), and transaminitis (18% vs. 10%), and there was a single mortality in each group.[154] OS was significantly longer among patients in the personalized dosimetry group who received a tumor dose >205 Gy versus those who received lower doses (median OS, 22.9 vs.10.3 months; $p = .001$).[155]

TARE has been evaluated as a primary therapy for HCC across various stages and has essentially replaced TACE as first-line transarterial therapy.[156] In the first randomized trial comparing TARE versus TACE in patients with BCLC stage A or B HCC (using conventional dosimetry), the time-to-progression was >26 months with TARE and 6.8 months after cTACE ($p = .001$) and toxicity was significantly lower, but there was no significant difference in OS (18.6 vs. 17.7 months). This trial importantly established radioembolization as preferable to TACE for transplantation-eligible patients to minimize the risk losing their candidacy because of progression.[157] In a more contemporary trial that randomized patients to TARE (using personalized dosimetry) or to DEB-TACE for early or intermediate, unresectable HCC, a significant survival benefit was demonstrated (30.2 vs. 15.6 months; $p = .006$).[158] Therefore, with this trial, radioembolization became the preferred transarterial therapy for both transplant and nontransplant candidates. Further studies of TARE using the radiation segmentectomy approach demonstrated even better outcomes. Lewandowski et al. retrospectively determined that radiation segmentectomy using a target tissue dose >190 Gy was comparable to curative-intent treatments in early stage HCC for solitary tumors ≤5 cm, and especially for lesions ≤3 cm.[150] The objective response rate was 90%, and 59% of patients had a complete response, with a median time to progression of 2.4 years. The median OS was 6.7 years with a 57% OS rate at 5 years and a 75% OS rate for tumors ≤3 cm. The 2021 LEGACY retrospective multicenter study by Salem et al. reported an 88.3% response rate for treatment-naive patients who had solitary HCC lesions ≤8 cm, with 62.2% showing a response duration of ≥6 months and a 3-year OS rate of 86.6%, which increased to 92.8% for patients who later underwent resection or LT.[159]

The SARAH and SIRveNIB multicenter randomized trials (ClinicalTrials.gov identifiers NCT10142442 and NCT01135056, respectively) compared TARE versus sorafenib in advanced HCC. The 2017 SARAH trial reported no difference in OS or PFS between the two treatments, but TARE demonstrated significantly better tolerability and fewer adverse events. The median OS was 8 months (95% CI, 6.7–9.9 months) in the TARE group versus 9.9 months (95% CI, 8.7–11.4 months) in the sorafenib group (TARE vs. sorafenib: HR, 1.15; 95% CI, 0.94–1.41; $p = .18$). At least one serious adverse event was reported in 174 of 226 patients (77%) in the TARE group and in 176 of 216 patients (82%) in the sorafenib group.[160] Similarly, the 2018 SIRveNIB trial indicated no difference in OS, time to progression, or

PFS, but TARE was tolerated better overall than sorafenib.[161] However, it is notable that both trials used conventional dosimetry rather than modern dosimetric methods that use the principles of higher dose to more limited regions. In a more contemporary trial examining the use of ablative dosing in 57 patients who had advanced HCC with portal venous invasion, the median OS with high-dose treatments was 45.3 months compared with 18.2 months when lower doses were used.[151] In another study using personalized dosimetry in 18 patients who had advanced HCC with portal invasion, multifocal, or large tumors and underwent resection after downstaging using TARE, the OS was 61.8 months, and 79% of the 14 patients who had vascular invasion exhibited complete pathologic necrosis of the intravascular tumor.[152]

In summary, based on the aggregate of data, TARE has a longer time to progression and a higher rate of complete pathologic necrosis than TACE and TAE, making it the preferable transarterial modality in both transplant and nontransplant candidates. TARE is also the primary treatment option for patients with vascular invasion. The use of personalized dosimetry with higher doses to tumor and lower doses to parenchyma is key to optimizing outcomes. However, TACE and TAE may be considered for patients who are poor TARE candidates.

Hepatic arterial infusion

Hepatic arterial infusion (HAI) chemotherapy most often entails the surgical implantation of a subcutaneous pump and catheter to deliver high-dose chemotherapy directly to the liver through the gastroduodenal artery.[162,163] This therapy has been used predominantly at Memorial Sloan Kettering Cancer Center over the past 5 decades but has recently expanded throughout the United States as well as internationally as a recognized treatment for colorectal liver metastases and intrahepatic cholangiocarcinoma.[163–167] Its role in the management of locally advanced HCC is much less clear, although recent data from China using HAI by means of percutaneously inserted catheters and intermittent drug delivery (rather than implantable, pump-based continuous infusion) suggest that HAI may be a valuable strategy for some patients. The phase 3 FOHAIC-1 trial (ClinicalTrials.gov identifier NCT03164382) randomized patients with previously untreated unresectable HCC to receive either HAI with fluorouracil, leucovorin, and oxaliplatin (FOLFOX) versus sorafenib. Patients who received treatment with HAI chemotherapy (liver-directed chemotherapy only, without any systemic therapy) had significantly improved OS compared with those who received sorafenib (median OS, 13.9 vs. 8.2 months; $p < .001$).[168] These findings were similar to another randomized clinical trial comparing HAI FOLFOX combined with sorafenib versus sorafenib alone among patients who had advanced HCC and portal vein invasion (median OS, 13.4 vs. 7.1 months; $p < .001$).[169]

More recently, Li et al. randomized patients with untreated yet unresectable HCC up to 7 cm to receive HAI FOLFOX versus TACE (epirubicin, lobaplatin, lipiodol, and polyvinyl alcohol particles). In their phase 3 trial, HAI FOLFOX improved OS (median OS, 23.1 vs. 16.1 months; $p < .001$) and progression-free survival (median PFS, 9.6 vs. 5.4 months; $p < .001$) compared with TACE.[170] A recent meta-analysis demonstrated that, compared with TACE, HAI chemotherapy as first-line therapy was associated with better OS (HR, 0.53; 95% CI, 0.40–0.69) and PFS (HR, 0.54; 95% CI, 0.40–0.72). Further subgroup analysis revealed that HAI chemotherapy may yield improved survival over TACE, regardless of tumor stage, especially in patients with advanced portal vein tumor thrombus.[171]

ABLATION

A multitude of ablative modalities exist, including heat-based RFA and microwave ablation (MWA), cold-based (cryoablation), nonthermal (irreversible electroporation), and chemical (ethanol), each selected based on anatomic considerations and institutional practice preferences and expertise.[172] Currently, MWA is the most commonly used thermal ablative modality because of technical considerations, including a shorter ablation time and less of a heat-sink effect near major vessels, compared with RFA. Although there is no absolute tumor size beyond which RFA/MWA should not be considered, the best outcomes are in patients who have one to three lesions <3 cm.[173] In addition to tumor size, tumor location also plays an important role in determining candidacy, including proximity to major bile ducts, diaphragm, gallbladder, and viscus structures. Image guidance for probe placement is typically performed using CT and/or US.

In a large, multicenter, retrospective series that included 139 patients who had HCC, local recurrence was observed in 12%, the median survival was 27 months, and tumor size >3 cm was associated with worse RFS.[174] In the first published RCT in 2010 comparing RFA versus resection in patients who had HCC within Milan criteria, the OS rate was higher with resection than with RFA (5-year OS, 76.7% vs. 54.8%; $p = .001$) as was PFS (5-year PFS, 51.3% vs. 28.7%; $p = .017$).[175] Since then, three additional RCTs were conducted comparing resection versus RFA, all of which demonstrated similar OS and PFS. Feng et al. randomized patients who had up to two HCC tumors measuring <4 cm to undergo either surgical resection or RFA. The 1-year, 3-year, and 5-year RFS rates were similar between the two groups (resection: 90.6%, 76.7%, and 61.1%, respectively; RFA: 86.2%, 66.6%, and 49.6%, respectively; $p = .122$), as were OS rates at 1 year, 2 years, and 3 years (resection: 96.0%, 87.6%, and 74.8%, respectively; RFA: 93.1%, 83.1%, and 67.2%, respectively; $p = .342$).[176] Ng et al. randomized patients who had HCC within Milan criteria to either RFA or resection, again demonstrating similar OS and PFS.[177] In the largest and most recent multicenter randomized trial published in 2022, Takayama et al. randomized 301 patients with up to three HCC nodules measuring up to 3 cm in greatest dimension to undergo resection or RFA, and no difference was demonstrated in RFS (median, 3.5 vs. 3.0 years; $p = .58$).[178] The converging outcomes

between RFA and resection may be attributed to improvements in techniques and technology because percutaneous RFA of the liver was first reported in 1995.[179] It is notable that these randomized studies excluded patients with significant portal hypertension.

Based on these data, RFA has been shown to yield similar OS as resection for patients who have a limited number of small HCCs, with lower morbidity and a shorter hospital stay (Figures 2 and 3). RFA can also be performed for patients who have portal hypertension, ascites, and varices, with significantly longer survival compared with untreated patients.[180] Although outcomes for both RFA and resection are similar, tumor location and patient characteristics (portal hypertension, cardiac disease, etc.) play an important role in determining candidacy for both ablation and resection. One of the advantages of ablation is its parenchymal-sparing nature, which is important in cirrhotic patients who are likely to develop additional HCC. Although no studies have been performed comparing microwave ablation versus resection, a meta-analysis reported that RFA and MWA have similar 1-year to 5-year OS, RFS, and local recurrence rates and fewer adverse events, whereas MWA had a significantly better 6-year OS rate.[181]

EXTERNAL BEAM RADIATION

Historically, external beam radiation therapy (EBRT) for HCC has been used cautiously because of the radiosensitivity of the liver and the technical inability to deliver conformal radiotherapy.[182] However, the development of more targeted modes of radiation delivery, namely, SBRT and proton-beam radiotherapy, led to the increasing consideration of EBRT as a therapeutic option for HCC with acceptable safety, decreased concern for radiation-induced liver injury, and improved cost effectiveness (Figures 2 and 3).[183,184] Multiple retrospective studies and clinical trial data have demonstrated similar local control rates between EBRT and other liver-directed therapies like RFA.[185,186] Indeed, SBRT has shown control rates ranging from 95% to 100% up to 1 or 2 years after treatment,[187–189] and it has also been used as a bridge to LT to provide tumor downstaging or stabilization of disease while waiting for an organ. It is important to note that these studies often underrepresent patients with CTP scores greater than B7; and, when included, they typically receive lower doses of radiation because of concerns about liver toxicity.[190] For this reason, caution should be exercised when treating patients with significant underlying hepatic dysfunction.

A large, intention-to-treat, retrospective study indicated a similar drop-out rate between SBRT, TACE, and ablation when these strategies were used to bridge patients to transplantation (16.7% in the SBRT group vs. 20.2% in the TACE group and 16.8% in the RFA group; $p = .7$). The respective 1-year, 3-year, and 5-year actuarial patient survival rates from the time of listing were 83%, 61%, and 61% in the SBRT group versus 86%, 61%, and 56% in the TACE group and 86%, 72%, and 61% in the RFA group ($p = .4$). The respective 1-year, 3-year, and 5-year survival rates from the time of transplantation were 83%, 75%, and 75% in the SBRT group versus 96%, 75%, and 69% in the TACE group and 95%, 81%, and 73% in the RFA group ($p = .7$).[191] iRECIST (modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics), a multicenter study, offered a more robust interpretation of HCC response after SBRT, leading to enhanced predictions of local tumor control and 1-year survival rates compared with traditional criteria.[192]

Despite its rise as non-invasive anticancer therapy that may be considered for curative-intent treatment of small HCC or to provide durable disease control in larger HCC tumors, randomized data for radiotherapy in the first-line setting are still lacking. To fill this knowledge gap, the SOCRATES-HCC study (Australian New Zealand Clinical Trials registry number ACTRN12621001444875) is the first active, randomized, multicenter trial to assess the safety, efficacy, and cost effectiveness of radiation compared with standard therapies as first-line treatment for unresectable, early stage HCC.[193] This study involves a collaboration among hepatology, interventional radiology, and radiation oncology groups across Australia, coordinated by the Trans Tasman Radiation Oncology Group (TROG Cancer Research). Finally, data from the NRG Oncology/RTOG 1112 trial (a randomized phase 3 study presented at the 2023 American Society of Clinical Oncology Gastrointestinal Cancers Symposium; ClinicalTrials.gov identifier NCT01730937) compared sorafenib versus SBRT followed by sorafenib in HCC: compared with sorafenib alone, SBRT significantly improved both OS and PFS in patients with HCC, with no observed increase in adverse events. More specifically, after adjusting for various factors, the median OS was improved from 12.3 months (sorafenib alone, 90% CI, 10.6–14.3 months) to 15.8 months (sorafenib plus SBRT, 90% CI, 11.4–19.2 months; HR, 0.72; 95% CI, 0.52–0.99; two-sided Cox $p = .042$). Median PFS was also improved from 5.5 months (sorafenib only, 95% CI, 3.4–6.3 months) to 9.2 months (sorafenib plus SBRT, 95% CI, 7.5–11.9 months; HR, 0.55; 95% CI, 0.40–0.75; two-sided $p = .0001$). In addition, there was a strong indication of a quality-of-life benefit at 6 months with SBRT.[194]

SYSTEMIC METASTATIC DISEASE

Although locoregional therapies may be delivered selectively with the intent to control hepatic disease burden (Figures 2 and 3), the cornerstone of therapy for advanced HCC is systemic therapy (see recommendation 1.1,[195–199] recommendation 1.2,[196–198,200–204] recommendation 2.1,[205–207] recommendation 2.2,[208,209] recommendation 2.3,[210–213], and recommendation 3.1[211] in Table 6).[197–216] This section summarizes data for TKIs as well as immunotherapy, the latter having transformed the care for patients with advanced HCC.

Tyrosine kinase inhibitors

Sorafenib, a multitargeted, orally active, small-molecule TKI that predominantly inhibits Raf kinase and vascular endothelial growth

TABLE 6 Systemic therapy for advanced hepatocellular carcinoma.

Systemic therapy	Mechanism of action
Atezolizumab	Anti–PD-L1 antibody
Bevacizumab	VEGF monoclonal antibody
Cabozantinib	Tyrosine kinase inhibitor that targets VEGFR-2, MET, KIT, AXL, and FLT3
Durvalumab	Anti–PD-L1 antibody
Ipilimumab	Anti–CTLA-4 antibody
Lenvatinib	MTKI that targets VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, FGFR-1, FGFR-2, FGFR-3, FGFR-4, KIT, and RET
Nivolumab	Anti–PD-1 receptor antibody
Pembrolizumab	Anti–PD-1 antibody
Ramucirumab	Anti-VEGFR2 antibody
Regorafenib	MTKI that targets EGFR and VEGF receptors
Sorafenib	MTKI that targets VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, KIT, RET, RAS/RAF/MAPK, and FLT-3
Tremelimumab	Anti–CTLA-4 antibody

Recommendations[a]		Systemic therapy	Note
First-line therapy	Recommendation 1.1 (Ren 2021[197], Abou-Alfa 2022,[198] Kelley 2022,[199] Llovet 2008,[200] Kudo 2018[201])	Atezolizumab + bevacizumab or durvalumab + tremelimumab	First-line treatment for patients with Child–Pugh class A and ECOG PS 0–1 advanced HCC
	Recommendation 1.2 (Abou-Alfa 2022,[198] Kelley 2022,[199] Llovet 2008,[200] Yau 2022,[202] Qin 2023,[203] Peng 2023,[204] Roessler 2023,[205] Alden 2023[206])	Sorafenib OR lenvatinib OR durvalumab	Where there are contraindications to recommendation 1.1
Second-line therapy	Recommendation 2.1 (Kim 2023,[207] Bruix 2017,[208] Abou-Alfa 2018[209])	Sorafenib OR lenvatinib OR cabozantinib OR ramucirumab	After first-line therapy with atezolizumab + bevacizumab, second-line therapy with a TKI or ramucirumab (AFP ≥400 ng/mL) is recommended
	Recommendation 2.2 (Zhu 2019[210] Finn 2020[211])	Sorafenib OR lenvatinib OR cabozantinib	After first-line therapy with durvalumab + tremelimumab, second-line therapy with a TKI is recommended
	Recommendation 2.3 (Qin 2021,2023,[212, 213] Finn 2022,[214] Topalian 2015[215])	Cabozantinib OR regorafenib OR ramucirumab OR nivolumab + ipilimumab OR durvalumab	After first-line therapy with sorafenib or lenvatinib, second-line therapy with another TKI (cabozantinib or regorafenib), ramucirumab (AFP ≥400 ng/mL), nivolumab + ipilimumab, or durvalumab may be recommended for appropriate candidates; atezolizumab + bevacizumab or durvalumab + tremelimumab may be considered for patients who may not have access to these therapies in the first-line setting and do not have contraindications to these combinations
Third-line therapy	Recommendation 3.1 (Finn 2020[211])	Third-line therapy may be considered in CTP A patients with good performance status using one of the agents listed previously that has a mechanism of action nonidentical to that of the previously received therapy	

Abbreviations: AFP, α-fetoprotein; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CTP A, Child–Turcotte–Pugh class A; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; MTKI, multitargeted tyrosine kinase receptor inhibitor; PD-1, programmed cell death protein-1; PD-L1, programmed death ligand 1; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

[a]Gordan JD, Kennedy EB, Abou-Alfa GK, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline update. *J Clin Oncol*. 2024;42 (15):1830-1850. 10.1200/JCO.23.02745.[216]

factor receptor (VEGFR) intracellular kinase, became the standard systemic therapy for patients with advanced HCC based on the SHARP randomized trial (ClinicalTrials.gov identifier NCT00105443).[200] Compared with patients who were randomized to placebo, those who were treated with sorafenib had a longer median OS (10.7 vs. 7.9 months; HR, 0.69; 95% CI, 0.55–0.87). There was no significant difference between the two groups regarding the median time to symptomatic progression (4.1 vs. 4.9 months, respectively; $p = .77$), although the median time to radiologic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group ($p < .001$).[200]

Lenvatinib is a modern TKI that inhibits VEGFR1–VEGFR3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT. The efficacy of lenvatinib for advanced HCC was evaluated in the REFLECT randomized noninferiority trial (ClinicalTrials.gov identifier NCT01761266), which compared it with sorafenib in 954 patients with unresectable HCC who had not received prior systemic therapy (CTP class A, 99%). Lenvatinib resulted in a noninferior OS compared with sorafenib (13.6 vs. 12.3 months; HR, 0.92; 95% CI, 0.79–1.06), although the objective response rate was higher (24% vs. 9%) and the median time to progression was longer (7.4 vs. 3.7 months; HR, 0.66; 95% CI, 0.57–0.77). Regarding toxicity, grade 3–4 hypertension was more common with lenvatinib (23% vs. 14%), whereas hand–foot–skin reactions (52% vs. 37% any grade, 11% vs. 3% grade ≥3) and alopecia (25% vs. 3%) were more frequent with sorafenib.[201] Based on these data, sorafenib and lenvatinib are considered interchangeable and may be used in the first-line or later line setting dictated by the patient's candidacy for more effective, modern-day treatment (e.g., immunotherapy; reviewed below).

Other TKIs have demonstrated a survival benefit compared with placebo in patients previously treated with sorafenib. RESORCE (ClinicalTrials.gov identifier NCT01774344) was a randomized, double-blinded, parallel-group, phase 3 trial that included patients with CTP A HCC who tolerated sorafenib but had disease progression. In this study, regorafenib improved OS compared with placebo (10.6 vs. 7.8 months, respectively; HR, 0.63; 95% CI, 0.50–0.79). Adverse events were reported in all regorafenib recipients (374 of 374 patients; 100%) and in 179 of 193 (93%) who received placebo.[208]

Cabozantinib was shown to significantly extend OS compared with placebo in a population that progressed after at least one line of treatment, including prior sorafenib. Compared with placebo, cabozantinib significantly improved OS (median, 10.2 vs. 8 months; HR, 0.76; 95% CI, 0.63–0.92). In addition, it was associated with an improvement in PFS (median, 5.2 vs. 1.9 months; HR, 0.44; 95% CI, 0.36–0.52) and a modest but higher objective response rate (4% vs. <1%; $p = .009$). Grade 3–4 adverse events occurred in 68% of patients in the cabozantinib group compared with 36% of patients in the placebo group.[209] The most frequent high-grade adverse events included palmar–plantar erythrodysesthesia (17% with cabozantinib vs. 0% with placebo), hypertension (16% vs. 2%, respectively), and elevated aspartate aminotransferase levels (12% vs. 7%, respectively).

The phase 3 randomized and placebo-controlled REACH-2 trial (ClinicalTrials.gov identifier NCT02435433) examined ramucirumab (an immunoglobulin-G1 VEGFR2 antagonist) in patients with advanced HCC who had either progressed on or could not tolerate sorafenib. Ramucirumab showed consistent, meaningful clinical efficacy without new safety concerns in patients with advanced HCC and AFP levels ≥400 ng/mL who had received treatments other than sorafenib. More specifically, the median OS was 8.5 months in the ramucirumab group (95% CI, 7.0–10.6 months) versus 7.3 months in the placebo group (95% CI, 5.4–9.1 months; HR, 0.710; 95% CI, 0.531–0.949; $p = .0199$), and PFS was 2.8 months (95% CI, 2.8–4.1 months) versus 1.6 months (95% CI, 1.5–2.7 months; HR, 0.452; 95% CI, 0.339–0.603; $p < .0001$), respectively. This study stands as one of the initial sequencing investigations for patients with advanced HCC who did not receive treatment with sorafenib.[214]

Immunotherapy

The most significant advancement in modern-day treatment of HCC has been the development and approval of immunotherapy, which has quickly become the standard of care for the treatment of patients with advanced HCC in the first-line and later-line settings (Table 6). Immunotherapies that inhibit the immune checkpoint interaction between programmed cell death protein-1 (PD-1) and programmed death-ligand 1 (PD-L1) have shown substantial survival benefit in some patients with metastatic carcinomas[215] and thus were hypothesized to play a role in the treatment of HCC because there is significant expression of PD-1 in the HCC tumor microenvironment.[217] The first suggestion that immunotherapy could be a relevant treatment for HCC came from CheckMate 040 (ClinicalTrials.gov identifier NCT01658878), a phase 1/2, open-label, noncomparative, dose-escalation, and expansion trial that included 148 patients. In this trial, nivolumab elicited a response rate of 20% and a median survival of 13 months. During the dose-escalation phase, nivolumab showed an acceptable safety profile and was generally well tolerated.[218]

A global, open-label, phase 3 trial included 501 patients with unresectable HCC and randomized them to atezolizumab (anti–PD-L1) and bevacizumab (anti-VEGF) together (now standard of care first-line therapy for patients with advanced HCC) versus sorafenib (the previous standard of care). The intention-to-treat analysis showed a HR of 0.58 for death (95% CI, 0.42–0.79; $p < .001$) with atezolizumab/bevacizumab versus sorafenib. The OS at 12 months was 67.2% (95% CI, 61.3%–73.1%) with atezolizumab/bevacizumab and 54.6% (95% CI, 45.2%–64.0%) with sorafenib. The median PFS was 6.8 months (95% CI, 5.7–8.3 months) and 4.3 months (95% CI, 4.0–5.6 months) in the respective groups (HR, 0.59; 95% CI, 0.47–0.76; $p < .001$).[219] Grade 3–4 adverse events occurred in 56.5% of 329 patients who received at least one dose of atezolizumab/bevacizumab and in 55.1% of 156 patients who received at least one dose of sorafenib.[219] Grade 3–4 hypertension was observed in 15.2% of patients in the atezolizumab/bevacizumab group, whereas other high-grade toxic effects were rare.

The benefit of immunotherapy-based regimens, specifically dual-checkpoint inhibition, was further supported by the HIMALAYA trial (ClinicalTrials.gov identifier NCT03298451), a phase 3, multicenter RCT that included 1171 patients with unresectable HCC and evaluated the STRIDE regimen (tremelimumab [anticytotoxic T-lymphocyte–associated protein 4 monoclonal antibody] with durvalumab [an anti–PD-L1 monoclonal antibody) versus durvalumab monotherapy versus sorafenib monotherapy as first-line treatment for patients with unresectable HCC. The OS with durvalumab monotherapy was noninferior to sorafenib (HR, 0.86; 95.67% CI, 0.73–1.03; noninferiority margin, 1.08), whereas the OS with STRIDE was 16.4 months versus only 13.8 months with sorafenib ($p = .0035$). The OS HR for STRIDE versus sorafenib was 0.78 (96.02% CI, 0.65–0.93; $p = .0035$), although the median PFS was not significantly different between the three groups. Grade 3–4 treatment-emergent adverse events occurred in 50.5% of patients with STRIDE (lipase increased in 6.2%, aspartate aminotransferase increased in 5.2%, and diarrhea increased in 4.4%), in 37.1% with durvalumab (aspartate aminotransferase increased in 6.7%, lipase increased in 4.1%, and alanine aminotransferase increased in 3.1%), and in 52.4% with sorafenib (palmar–plantar erythrodysesthesia syndrome in 9.1%, hypertension in 6.1%, diarrhea in 4.3%).[198] The 4-year follow-up of the trial indicated that the OS HR for STRIDE versus sorafenib remained 0.78 (95% CI, 0.67–0.92); the OS rate at 36 and 48 months for STRIDE was 30.7% and 25.2%, respectively, compared with 19.8% and 15.1%, respectively, for sorafenib.[220]

Two additional immunotherapy-based regimens being investigated were highlighted at the 2024 American Society of Clinical Oncology Annual Meeting. The initial findings from CheckMate 9DW, which compared ipilimumab plus nivolumab versus lenvatinib or sorafenib as first-line treatment for unresectable HCC indicate that the combination of ipilimumab plus nivolumab resulted in a statistically significant improvement in OS compared with lenvatinib or sorafenib, along with a higher objective response rate, more durable response, and a manageable safety profile. More specifically, the median OS was 23.7 months with ipilimumab plus nivolumab versus 20.6 months with lenvatinib or sorafenib (HR, 0.79; 95% CI, 0.65–0.96; $p = .0180$)[128] Furthermore, the final OS analysis of the phase 3 CARES-310 study (ClinicalTrials.gov identifier NCT03764293) was presented, evaluating camrelizumab plus rivoceranib versus sorafenib as first-line therapy for unresectable HCC. Camrelizumab plus rivoceranib continued to show a clinically meaningful improvement in survival over sorafenib, with a manageable safety profile, supporting it as a new first-line treatment option for unresectable HCC. The median OS was significantly prolonged with camrelizumab plus rivoceranib versus sorafenib (23.8 months [95% CI, 20.6–27.2 months] vs. 15.2 months [95% CI, 13.2–18.5 months]; HR, 0.64; 95% CI, 0.52–0.79; one-sided $p < .0001$).[221]

Monotherapies have demonstrated either noninferiority or, in certain contexts, superiority to sorafenib and may represent a viable treatment option for patients who are unsuitable for the more toxic dual-therapy regimens like atezolizumab/bevacizumab and tremelimumab/durvalumab (Table 6). Such data include the single-arm phase 2 KEYNOTE-224 trial (ClinicalTrials.gov identifier NCT02702414), which demonstrated that first-line, single-agent pembrolizumab in patients with advanced HCC achieved an objective response rate of 16% (all partial responses) and a median duration of response of 16 months (range, 3 to >24 months). The median PFS and OS were 4 and 17 months, respectively.[222] Similarly, nivolumab in the first-line setting was directly compared with sorafenib in the phase 3 CheckMate 459 trial (ClinicalTrials.gov identifier NCT02576509), which enrolled 743 treatment-naive patients with advanced HCC. In that trial, nivolumab yielded a two-fold higher objective response rate (15% vs. 7%) and more complete responses (4% vs. 1%); however, PFS (median, 3.7 vs. 3.8 months) and OS (median, 16.4 vs. 14.7 months; HR, 0.85; 95% CI, 0.72–1.02) were similar. Grade 3–4 treatment-related serious adverse events were also similar between groups (nivolumab 12% vs sorafenib 11%), as were the rates of treatment discontinuation because of toxicity.[204] A summary of guideline-based recommendations are included in Table 6, which are often dictated by patient-specific, liver-specific, and disease-specific factors.

MULTIMODAL MANAGEMENT OF ADVANCED HCC—COMBINING LIVER-DIRECTED THERAPIES WITH SYSTEMIC THERAPY

For some patients, particularly those with locally advanced HCC confined to the liver, combining liver-directed therapies with systemic therapies is a promising treatment paradigm that is gaining popularity (Figures 2 and 3). The EMERALD-1 phase 3 RCT (ClinicalTrials.gov identifier NCT03778957) evaluated TACE combined with durvalumab with or without bevacizumab for patients who had CTP stage A-B7 cirrhosis and HCC confined to the liver.[223] The trial had three therapeutic arms: TACE only, TACE with durvalumab, and TACE with durvalumab and bevacizumab.[223] The trial included 616 patients and demonstrated that PFS was significantly improved for TACE with durvalumab and bevacizumab versus TACE (median PFS, 15.0 vs. 8.2 months; HR, 0.77; 95% CI, 0.61–0.98; $p = .032$).[223] Interestingly, the secondary end point, which compared PFS between TACE plus durvalumab and TACE alone, was not met (100 vs. 8.2 months; HR, 0.94; $p = .638$).[223] Response rates were concordantly improved from 29.6% to 43.6%, and the median time to progression was improved from 10 months to 22 months when durvalumab and bevacizumab were added to TACE.[223] Despite more intense therapy, the combination of TACE with systemic therapy did not result in an increase in adverse events. Similarly, the recently released results from LEAP-012—a randomized, multicenter, double-blind, phase 3 trial that included 480 patients with unresectable HCC and assessed lenvatinib plus pembrolizumab with TACE versus placebo with TACE in intermediate-stage HCC (ClinicalTrials.gov identifier NCT04246177)—demonstrated a statistically significant and clinically meaningful improvement in PFS compared with the placebo/TACE regimen (HR, 0.66; 95% CI, 0.51–0.84; $p = .0002$), with a

median PFS of 14.6 months (95% CI, 12.6–16.7 months) versus 10.0 months (95% CI, 8.1–12.2 months).[224]

Combining immunotherapy with TARE has also been investigated and may have even greater potential given the suspected immunogenic properties of yttrium-90. In a phase 1/2a study that combined TARE with durvalumab for patients with liver-confined, locally advanced HCC, inclusive of patients with BCLC stage B and C disease, the median time to progression was 15.2 months, the median OS was not reached, and nearly 60% of patients were alive at 18 months.[225] Response rates with this combination were also encouraging, with a complete response in 29.2% of patients and a partial response in 54.2%, yielding an overall response rate of 83.4%. Importantly, grade ≥3 adverse events were observed in only 8.7% of patients. Similarly, in another small study, 27 patients with locally advanced HCC who were not eligible for transplant or resection were treated with TARE and pembrolizumab. The primary end point was 6-month PFS, with 55.6% of patients achieving this outcome, and the median PFS was nearly 10 months. The ORR was 30.8%, and the disease control rate was 84.6%.[226] Finally, the CA209-678 phase 2 trial (ClinicalTrials.gov identifier NCT03033446) demonstrated that TARE followed by nivolumab achieved a median OS of 16.9 months, although the median PFS was only 3.6 months.[227] Intrahepatic tumors had a higher response rate of 43.5%, indicating potential synergy, with TARE possibly enhancing the effectiveness of PD-1 inhibitors.[227]

Taken together, these data suggest that combining TARE with immunotherapy has a promising response rate and safety profile with a signal toward survival benefit and warrants ongoing evaluation.[225] Furthermore, given the signal for efficacy in patients with liver-confined yet advanced HCC, combining modalities may also have relevance for patients with distant disease but significant hepatic disease burden, with the goal of liver-directed therapy to control hepatic disease, which is thought to be the primary driver of prognosis. It is anticipated that such a treatment paradigm may become commonplace in the future.

Patients with HCC understand that optimal care often comes from multidisciplinary teams. However, access to multimodal care can be uneven, including strategies such as liver-directed therapies in combination with systemic therapies. Patients living far from major or academic centers or without adequate insurance may struggle to receive the full range of treatments. Thus, advocacy for equitable access to such therapies and support throughout a patient's treatment journey is critical. Telehealth hepatology consultations for HCC effectively coordinate surveillance, communicate treatment decisions, and are associated with outcomes similar to those of standard consultations.[228,229]

EMERGING THERAPIES FOR HCC

Emerging therapies for HCC have been advancing rapidly. Several new approaches are being explored in clinical trials, aiming to improve patient outcomes. Antibody–drug conjugates are emerging as an advanced chemotherapeutic option designed to selectively destroy neoplastic cells with minimal toxicity to noncancerous cells. Studies indicate enormous potential for antibody–drug conjugates that target GPC3, CD24, and other tumor-associated antigens in HCC due to their high tumor-specific expression and have demonstrated potential relevance in preclinical evaluations (see Table S2).[230] Another emerging field in the management of advanced HCC is chimeric antigen receptor T-cell therapy. Currently, relevant research focuses on GPC3-targeted therapy, evaluating multiple molecules, mainly in a preclinical setting, demonstrating significant antitumor activity and prolonged survival in animal models of HCC.[231] Moreover, given the immunosuppressive liver tumor microenvironment, combining chimeric antigen receptor T-cell therapy with ICIs or locoregional therapies might help enhance the activity of chimeric antigen receptor T-cell therapyy.[232]

UTILIZING MULTIDISCIPLINARY TEAMS FOR INDIVIDUALIZED DECISION MAKING

Considering the large number of treatment options available for patients with HCC, the methodology for deciding the optimal treatment for any given patient is particularly challenging. Historically, numerous algorithms were created to help guide treatment decisions[38,65,233] However, algorithms are increasingly becoming outdated, incomplete, and complicated because of the growing number of treatment options and combination therapies. Although many treatments and combination therapies have highly promising results, there is a paucity of randomized studies that compare outcomes between the various treatments. Because most patients with HCC have various degrees of cirrhosis, they represent a particularly complex subset of patients who have cancer. Essentially, all treatment options adversely affect hepatic reserve to some degree, making it essential to balance effective cancer control with the preservation of liver function—particularly because between one quarter to one third of patients with HCC die of competing risks, specifically underlying liver-related complications, rather than HCC.[234] Therefore, although the primary goal of cancer therapies is to eradicate or manage HCC, maintaining liver function is equally critical for improving patient outcomes. Because LT produces the best outcomes for the majority of patients, the goals of treatment are not only to preserve liver function and control tumor but also to optimize transplantation candidacy. Although no algorithm can accurately and comprehensively capture the complexities of the patients and treatments, multidisciplinary tumor boards have emerged as a critical tool to guide optimal decision making that often now supersedes most algorithms. These teams typically consist of transplant hepatologists, gastroenterologists, hepatobiliary surgeons, transplant surgeons, diagnostic radiologists, interventional radiologists, medical oncologists, and radiation oncologists. A multimodal treatment approach for HCC from a patient's perspective involves not only dealing with the medical aspects of the disease but also navigating the physical, emotional, and practical challenges that arise during treatment. Patient-centered considerations are essential

when contemplating multimodal therapy. Patients with HCC often face a bleak outlook, so the opportunity to receive multiple, targeted treatment options brings a sense of hope. Multimodal treatments are seen as a way to maximize the chances of tumor reduction or elimination, potentially extend life expectancy, and offer personalized care tailored to individual tumor characteristics. Many patients with HCC prioritize quality of life as an even higher priority than survival. Patients want to maintain as much normalcy as possible and to be able to perform daily activities, spend time with loved ones, and retain some control over their bodies and choices. A multimodal treatment approach may offer the potential to extend life, but it can also compromise a patient's physical and emotional state.

With the involvement of specialty teams, all options available locally can be explored and discussed. Each specialist can weigh in on the expected outcomes with the treatment(s) from their specialty because numerous tumor and patient factors must be considered; then, consensus may be achieved for optimal treatment. In many cases, equivalent options may be available. In these cases, patients can be educated and counseled by pertinent specialists, and the patient can decide what best fits their goals, desires, and social situation. Numerous studies have analyzed patient outcomes when triaged through a multidisciplinary tumor board. In a retrospective study comparing patients managed through a multidisciplinary tumor board versus those who were not, patients managed via a tumor board had significantly higher survival: 19.1 versus 7.6 months; $p < .0001$.[235] Survival benefits with the use of a multidisciplinary clinic have been shown to persist even in multivariate analysis after adjusting for BCLC stage and receipt of curative-intent treatment.[236] Patients also presented at an earlier tumor stage ($p = .007$), with lower AFP levels ($p = .007$), and with a greater odds of HCC treatment ($p < .0001$). In a different study, patients undergoing imaging surveillance with a multidisciplinary clinic review were more likely to receive treatment with ablation or resection ($p = .006$) or with LT ($p = .001$) and were less likely to develop tumor progression ($p = .005$).[237]

Patients value clear communication and understanding of each treatment option. They want to know:

- How treatments work (e.g., how immunotherapy boosts the immune system or how chemotherapy targets cancer cells);
- Possible side effects and risks for both short-term and long-term; and
- Potential benefits in terms of survival, quality of life, and symptom management.

Many patients appreciate a balanced view in which the benefits of multiple treatments are weighed against their side effects and likely effect on day-to-day life, including:

- *Financial strain* because of the high cost of newer therapies (like targeted treatments and immunotherapy) and frequent medical visits; and
- *Emotional strain* from uncertainty, fear of treatment failure, and distress over side effects.

Patients appreciate psychosocial support services, such as counseling, support groups, or financial navigators, to help manage these challenges. They also desire health care providers who are empathetic and open to discussing the full scope of what they are experiencing.

Patients often report that the side effects of treatment, including fatigue, weight loss, nausea, liver complications, and mental health struggles, can be as challenging as the disease itself. A multimodal treatment approach, although potentially effective, can intensify these side effects because each therapy comes with its own set of risks (e.g., immunotherapy-related fatigue, chemotherapy-related nausea). In addition, combining treatments may lead to cumulative side effects, affecting physical and emotional well-being. For patients, the care team must support them in managing these side effects, providing clear strategies to alleviate discomfort, monitoring for early signs of complications, and providing emotional support to handle the mental toll. Finally, some patients may reach a point at which curative treatments are no longer effective, and they shift their focus to palliative care. A multimodal approach can integrate pain management, emotional and psychological support, and efforts to improve overall well-being in the final stages of the disease. In this phase, patients often want the care team to focus on quality of life rather than aggressive treatments that might not provide meaningful benefits.

In summary, although a multimodal treatment approach offers many potential benefits, patients must navigate a complex landscape of medical, emotional, and logistical challenges. Their priorities can shift throughout their disease, so health care providers must remain flexible, communicative, and supportive, ensuring that the treatment approach aligns with the patient's individual goals and needs.

CONCLUSIONS

In an ideal setting, all patients with HCC should be treated within a multidisciplinary setting focused on collaboration among surgeons, medical oncologists, radiation oncologists, interventional radiologists, and hepatologists to provide precision care and achieve optimal outcomes. Treatment paradigms must consider both patient-related and tumor-related factors, such as the extent of liver disease, which is often the primary driver of morbidity and mortality. Surgical treatment, either resection or transplantation, remains the best option for a cure in patients who are operable. The advent of more effective systemic and locoregional therapies has also facilitated prolonged survival among patients with advanced disease, as well as allowed patients to undergo surgical intervention who otherwise would have disease that is considered inoperable. BCLC and Milan criteria have standardized HCC management, offering a structured approach for the prognostic evaluation and treatment of patients with HCC. In the era of

precision medicine, therapeutic decision making should be individualized (by a multidisciplinary tumor board) rather than dictated simply by stage, with careful consideration when weighing the risks and benefits of a particular treatment and its toxicity profile and associated effect on quality of life. We support a *multiparametric therapeutic approach* that integrates a comprehensive assessment of clinical factors, biomarkers, technical feasibility, and resource availability.

CONFLICT OF INTEREST STATEMENT

Manisha Palta reports grants/contracts from Merck and Varian Medical Systems; and personal/consulting fees from Syntactx, Varian Medical Systems, and Voxelmetric outside the submitted work. Michael A. Morse reports personal/consulting fees from AstraZeneca, Eisai, Exelixis, Genentech, Servier Pharmaceuticals LLC, and Taiho Oncology Inc. outside the submitted work. The remaining authors disclosed no conflicts of interest.

ORCID

Dimitrios Moris https://orcid.org/0000-0002-5276-0699
Alessandro Martinino https://orcid.org/0000-0002-4016-534X
Andrew Barbas https://orcid.org/0000-0003-3476-2313
Debra Sudan https://orcid.org/0000-0003-4315-4459
Charles Kim https://orcid.org/0000-0002-8687-1522
Mustafa Bashir https://orcid.org/0000-0001-8800-5057
Manisha Palta https://orcid.org/0000-0002-9085-9075
Michael A. Morse https://orcid.org/0000-0002-5725-4533
Michael E. Lidsky https://orcid.org/0000-0003-0500-2016

REFERENCES

1. Beal EW, Tumin D, Kabir A, et al. Cohort contributions to race- and gender-specific trends in the incidence of hepatocellular carcinoma in the USA. *World J Surg*. 2018;42(3):835-840. doi:10.1007/s00268-017-4194-1
2. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol*. 2021;18(4):223-238. doi:10.1038/s41575-020-00381-6
3. Dimitroulis D, Damaskos C, Valsami S, et al. From diagnosis to treatment of hepatocellular carcinoma: an epidemic problem for both developed and developing world. *World J Gastroenterol*. 2017;23(29):5282-5294. doi:10.3748/wjg.v23.i29.5282
4. Llovet JM, Castet F, Heikenwalder M, et al. Immunotherapies for hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2022;19(3):151-172. doi:10.1038/s41571-021-00573-2
5. Ferlay J, Ervik M, Lam F, et al., eds. *Global Cancer Observatory: Cancer Today—Liver and intrahepatic bile duct*. International Agency for Research on Cancer; 2022. Accessed 18 March 2024. https://gco.iarc.who.int/media/globocan/factsheets/cancers/11-liver-and-intrahepatic-bile-ducts-fact-sheet.pdf
6. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin*. 2024;74(1):12-49. doi:10.3322/caac.21820
7. Petrick JL, Florio AA, Znaor A, et al. International trends in hepatocellular carcinoma incidence, 1978–2012. *Int J Cancer*. 2020;147(2):317-330. doi:10.1002/ijc.32723
8. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. *Hepatology*. 2021;73(suppl 1):4-13. doi:10.1002/hep.31288
9. McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. *Clin Liver Dis*. 2015;19(2):223-238. doi:10.1016/j.cld.2015.01.001
10. Akinyemiju T, Abera S, Ahmed M, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level. *JAMA Oncol*. 2017;3(12):1683-1691. doi:10.1001/jamaoncol.2017.3055
11. Yang JD, Hainaut P, Gores GJ, Amadou A, Plymoth A, Roberts LR. A global view of hepatocellular carcinoma: trends, risk, prevention and management. *Nat Rev Gastroenterol Hepatol*. 2019;16(10):589-604. doi:10.1038/s41575-019-0186-y
12. Yang J, Pan G, Guan L, et al. The burden of primary liver cancer caused by specific etiologies from 1990 to 2019 at the global, regional, and national levels. *Cancer Med*. 2022;11(5):1357-1370. doi:10.1002/cam4.4530
13. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res*. 2014;74(11):2913-2921. doi:10.1158/0008-5472.CAN-14-0155
14. Rumgay H, Arnold M, Ferlay J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. *J Hepatol*. 2022;77(6):1598-1606. doi:10.1016/j.jhep.2022.08.021
15. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. *Nat Rev Dis Primers*. 2021;7(1):6. doi:10.1038/s41572-020-00240-3
16. Abboud Y, Ismail M, Khan H, et al. Hepatocellular carcinoma incidence and mortality in the USA by sex, age, and race: a nationwide analysis of two decades. *J Clin Transl Hepatol*. 2024;12(2):172-181. doi:10.14218/JCTH.2023.00356
17. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69(1):182-236. doi:10.1016/j.jhep.2018.03.019
18. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2018;68(2):723-750. doi:10.1002/hep.29913
19. Trinchet JC, Bourcier V, Chaffaut C, et al. Complications and competing risks of death in compensated viral cirrhosis (ANRS CO12 CirVir prospective cohort). *Hepatology*. 2015;62(3):737-750. doi:10.1002/hep.27743
20. Toh MR, Wong EYT, Wong SH, et al. Global epidemiology and genetics of hepatocellular carcinoma. *Gastroenterology*. 2023;164(5):766-782. doi:10.1053/j.gastro.2023.01.033
21. Jain MK, Rich NE, Ahn C, et al. Evaluation of a multifaceted intervention to reduce health disparities in hepatitis C screening: a pre-post analysis. *Hepatology*. 2019;70(1):40-50. doi:10.1002/hep.30638
22. GDB 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1204-1222. doi:10.1016/S0140-6736(20)30925-9
23. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer*. 2015;112(3):580-593. doi:10.1038/bjc.2014.579
24. Turati F, Galeone C, Rota M, et al. Alcohol and liver cancer: a systematic review and meta-analysis of prospective studies. *Ann Oncol*. 2014;25(8):1526-1535. doi:10.1093/annonc/mdu020
25. Karim MA, Singal AG, Kum HC, et al. Clinical characteristics and outcomes of nonalcoholic fatty liver disease-associated hepatocellular carcinoma in the United States. *Clin Gastroenterol Hepatol*. 2023;21(3):670-680.e18. doi:10.1016/j.cgh.2022.03.010

26. Costentin CE, Mourad A, Lahmek P, et al. Hepatocellular carcinoma is diagnosed at a later stage in alcoholic patients: results of a prospective, nationwide study. *Cancer*. 2018;124(9):1964-1972. doi:10.1002/cncr.31215
27. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology*. 2018;67(1):123-133. doi:10.1002/hep.29466
28. Tan DJH, Ng CH, Lin SY, et al. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. *Lancet Oncol*. 2022;23(4):521-539. doi:10.1016/S1470-2045(22)00078-X
29. Balakrishnan M, Patel P, Dunn-Valadez S, et al. Women have a lower risk of nonalcoholic fatty liver disease but a higher risk of progression vs men: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2021;19(1):61-71.e15. doi:10.1016/j.cgh.2020.04.067
30. Galy B, Conrad M, Muckenthaler M. Mechanisms controlling cellular and systemic iron homeostasis. *Nat Rev Mol Cell Biol*. 2024;25(2):133-155. doi:10.1038/s41580-023-00648-1
31. Fillebeen C, Charlebois E, Wagner J, et al. Transferrin receptor 1 controls systemic iron homeostasis by fine-tuning hepcidin expression to hepatocellular iron load. *Blood*. 2019;133(4):344-355. doi:10.1182/blood-2018-05-850404
32. Brissot P, Pietrangelo A, Adams PC, de Graaff B, McLaren CE, Loréal O. Haemochromatosis. *Nat Rev Dis Primers*. 2018;4(1):18016. doi:10.1038/nrdp.2018.16
33. Hsu CC, Senussi NH, Fertrin KY, Kowdley KV. Iron overload disorders. *Hepatol Commun*. 2022;6(8):1842-1854. doi:10.1002/hep4.2012
34. Kowdley KV. Iron, hemochromatosis, and hepatocellular carcinoma. *Gastroenterology*. 2004;127(5 suppl 1):S79-S86. doi:10.1016/j.gastro.2004.09.019
35. Niu Y, Fan S, Luo Q, et al. Interaction of hepatitis B virus X protein with the pregnane X receptor enhances the synergistic effects of aflatoxin B1 and hepatitis B virus on promoting hepatocarcinogenesis. *J Clin Transl Hepatol*. 2021;9(4):466-476. doi:10.14218/JCTH.2021.00036
36. Kew MC. Synergistic interaction between aflatoxin B1 and hepatitis B virus in hepatocarcinogenesis. *Liver Int*. 2003;23(6):405-409. doi:10.1111/j.1478-3231.2003.00869.x
37. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet*. 2018;391(10127):1301-1314. doi:10.1016/S0140-6736(18)30010-2
38. Benson AB, D'Angelica MI, Abbott DE, et al. Hepatobiliary Cancers, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2021;19(5):541-565. doi:10.6004/jnccn.2021.0022
39. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology*. 2018;67(1):358-380. doi:10.1002/hep.29086
40. Kokudo N, Hasegawa K, Akahane M, et al. Evidence-based clinical practice guidelines for hepatocellular carcinoma: the Japan Society of Hepatology 2013 update (3rd JSH-HCC guidelines). *Hepatol Res*. 2015;45(2):e12464. doi:10.1111/hepr.12464
41. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. *Hepatol Int*. 2017;11(4):317-370. doi:10.1007/s12072-017-9799-9
42. American College of Radiology (ACR). *LI-RADS*. ACR; 2024. Accessed July 29, 2024. https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Reporting-and-Data-Systems/LI-RADS
43. Choi JY, Lee JM, Sirlin CB. CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part I. Development, growth, and spread: key pathologic and imaging aspects. *Radiology*. 2014;272(3):635-654. doi:10.1148/radiol.14132361
44. Narsinh KH, Cui J, Papadatos D, Sirlin CB, Santillan CS. Hepatocarcinogenesis and LI-RADS. *Abdom Radiol (NY)*. 2018;43(1):158-168. doi:10.1007/s00261-017-1409-8
45. Chartampilas E, Rafailidis V, Georgopoulou V, Kalarakis G, Hatzidakis A, Prassopoulos P. Current imaging diagnosis of hepatocellular carcinoma. *Cancers (Basel)*. 2022;14(16):3997. doi:10.3390/cancers14163997
46. Zhao C, Dai H, Shao J, et al. Accuracy of various forms of contrast-enhanced MRI for diagnosing hepatocellular carcinoma: a systematic review and meta-analysis. *Front Oncol*. 2021;11:680691. doi:10.3389/fonc.2021.680691
47. Rimola J, Forner A, Tremosini S, et al. Non-invasive diagnosis of hepatocellular carcinoma ≤2 cm in cirrhosis. Diagnostic accuracy assessing fat, capsule and signal intensity at dynamic MRI. *J Hepatol*. 2012;56(6):1317-1323. doi:10.1016/j.jhep.2012.01.004
48. Semaan S, Vietti Violi N, Lewis S, et al. Hepatocellular carcinoma detection in liver cirrhosis: diagnostic performance of contrast-enhanced CT vs. MRI with extracellular contrast vs. gadoxetic acid. *Eur Radiol*. 2020;30(2):1020-1030. doi:10.1007/s00330-019-06458-4
49. Hanna RF, Miloushev VZ, Tang A, et al. Comparative 13-year meta-analysis of the sensitivity and positive predictive value of ultrasound, CT, and MRI for detecting hepatocellular carcinoma. *Abdom Radiol (NY)*. 2016;41(1):71-90. doi:10.1007/s00261-015-0592-8
50. Roberts LR, Sirlin CB, Zaiem F, et al. Imaging for the diagnosis of hepatocellular carcinoma: a systematic review and meta-analysis. *Hepatology*. 2018;67(1):401-421. doi:10.1002/hep.29487
51. Aubé C, Oberti F, Lonjon J, et al. EASL and AASLD recommendations for the diagnosis of HCC to the test of daily practice. *Liver Int*. 2017;37(10):1515-1525. doi:10.1111/liv.13429
52. Tang M, Li Y, Lin Z, et al. Hepatic nodules with arterial phase hyperenhancement and washout on enhanced computed tomography/magnetic resonance imaging: how to avoid pitfalls. *Abdom Radiol (NY)*. 2020;45(11):3730-3742. doi:10.1007/s00261-020-02560-0
53. Huang B, Wu L, Lu XY, et al. Small intrahepatic cholangiocarcinoma and hepatocellular carcinoma in cirrhotic livers may share similar enhancement patterns at multiphase dynamic MR imaging. *Radiology*. 2016;281(1):150-157. doi:10.1148/radiol.2016151205
54. Xu J, Igarashi S, Sasaki M, et al. Intrahepatic cholangiocarcinomas in cirrhosis are hypervascular in comparison with those in normal livers. *Liver Int*. 2012;32(7):1156-1164. doi:10.1111/j.1478-3231.2012.02783.x
55. Chernyak V, Fowler KJ, Kamaya A, et al. Liver Imaging Reporting and Data System (LI-RADS) version 2018: imaging of hepatocellular carcinoma in at-risk patients. *Radiology*. 2018;289(3):816-830. doi:10.1148/radiol.2018181494
56. Rich NE, Chernyak V. Standardizing liver imaging reporting and interpretation: LI-RADS and beyond. *Hepatol Commun*. 2023;7(7):e00186. doi:10.1097/HC9.0000000000000186
57. Lehrich BM, Zhang J, Monga SP, Dhanasekaran R. Battle of the biopsies: role of tissue and liquid biopsy in hepatocellular carcinoma. *J Hepatol*. 2024;80(3):515-530. doi:10.1016/j.jhep.2023.11.030
58. Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(suppl 4):iv238-iv255. doi:10.1093/annonc/mdy308
59. Torbenson MS. Hepatocellular carcinoma: making sense of morphological heterogeneity, growth patterns, and subtypes. *Hum Pathol*. 2021;112:86-101. doi:10.1016/j.humpath.2020.12.009

60. Calderaro J, Ziol M, Paradis V, Zucman-Rossi J. Molecular and histological correlations in liver cancer. *J Hepatol*. 2019;71(3):616-630. doi:10.1016/j.jhep.2019.06.001
61. Torbenson MS. Morphologic subtypes of hepatocellular carcinoma. *Gastroenterol Clin North Am*. 2017;46(2):365-391. doi:10.1016/j.gtc.2017.01.009
62. Dahdaleh FS, Naffouje SA, Sherman SK, Kamarajah SK, Salti GI. Tissue diagnosis is associated with worse survival in hepatocellular carcinoma: a National Cancer Database analysis. *Am Surg*. 2022;88(6):1234-1243. doi:10.1177/0003134821991983
63. Amin MB, Greene FL, Edge SB, et al. The eighth edition AJCC Cancer Staging Manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA Cancer J Clin*. 2017;67(2):93-99. doi:10.3322/caac.21388
64. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer*. 1985;56(4):918-928. doi:10.1002/1097-0142(19850815)56:4<918::aid-cncr2820560437>3.0.co;2-e
65. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol*. 2022;76(3):681-693. doi:10.1016/j.jhep.2021.11.018
66. Daniele B, Annunziata M, Barletta E, Tinessa V, Di Maio M. Cancer of the Liver Italian Program (CLIP) score for staging hepatocellular carcinoma. *Hepatol Res*. 2007;37(suppl 2):S206-S209. doi:10.1111/j.1872-034X.2007.00186.x
67. Llovet JM, Villanueva A, Marrero JA, et al. Trial design and endpoints in hepatocellular carcinoma: AASLD consensus conference. *Hepatology*. 2021;73(suppl 1):158-191. doi:10.1002/hep.31327
68. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis*. 1999;19(3):329-338. doi:10.1055/s-2007-1007122
69. Tsilimigras DI, Bagante F, Sahara K, et al. Prognosis after resection of Barcelona Clinic Liver Cancer (BCLC) stage 0, A, and B hepatocellular carcinoma: a comprehensive assessment of the current BCLC classification. *Ann Surg Oncol*. 2019;26(11):3693-3700. doi:10.1245/s10434-019-07580-9
70. Kamiyama T, Orimo T, Wakayama K, et al. Survival outcomes of hepatectomy for stage B hepatocellular carcinoma in the BCLC classification. *World J Surg Oncol*. 2017;15(1):156. doi:10.1186/s12957-017-1229-x
71. Wang P, Zhang D, Fang C, et al. Partial hepatectomy vs. transcatheter arterial chemoembolization for multiple hepatocellular carcinomas of BCLC-B stage: a meta-analysis of high-quality studies. *Eur J Surg Oncol*. 2022;48(8):1685-1691. doi:10.1016/j.ejso.2022.04.017
72. Yin L, Li H, Li AJ, et al. Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan criteria: a RCT. *J Hepatol*. 2014;61(1):82-88. doi:10.1016/j.jhep.2014.03.012
73. Serper M, Taddei TH, Mehta R, et al. Association of provider specialty and multidisciplinary care with hepatocellular carcinoma treatment and mortality. *Gastroenterology*. 2017;152(8):1954-1964. doi:10.1053/j.gastro.2017.02.040
74. Vauthey JN, Klimstra D, Franceschi D, et al. Factors affecting long-term outcome after hepatic resection for hepatocellular carcinoma. *Am J Surg*. 1995;169(1):28-34; discussion 34-35. doi:10.1016/s0002-9610(99)80106-8
75. Bruix J, Castells A, Bosch J, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. *Gastroenterology*. 1996;111(4):1018-1022. doi:10.1016/s0016-5085(96)70070-7
76. Cucchetti A, Zhong J, Berhane S, et al. The chances of hepatic resection curing hepatocellular carcinoma. *J Hepatol*. 2020;72(4):711-717. doi:10.1016/j.jhep.2019.11.016
77. Pinna AD, Yang T, Mazzaferro V, et al. Liver transplantation and hepatic resection can achieve cure for hepatocellular carcinoma. *Ann Surg*. 2018;268(5):868-875. doi:10.1097/SLA.0000000000002889
78. Tsilimigras DI, Bagante F, Moris D, et al. Defining the chance of cure after resection for hepatocellular carcinoma within and beyond the Barcelona Clinic Liver Cancer guidelines: a multi-institutional analysis of 1,010 patients. *Surgery*. 2019;166(6):967-974. doi:10.1016/j.surg.2019.08.010
79. Chapman WC, Klintmalm G, Hemming A, et al. Surgical treatment of hepatocellular carcinoma in North America: can hepatic resection still be justified? *J Am Coll Surg*. 2015;220(4):628-637. doi:10.1016/j.jamcollsurg.2014.12.030
80. Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. *Ann Surg*. 1999;229(6):790-799; discussion 799-800. doi:10.1097/00000658-199906000-00005
81. Poon RTP, Fan ST, Lo CM, et al. Extended hepatic resection for hepatocellular carcinoma in patients with cirrhosis: is it justified? *Ann Surg*. 2002;236(5):602-611. doi:10.1097/00000658-200211000-00010
82. Famularo S, Ceresoli M, Giani A, et al. Is it just a matter of surgical extension to achieve the cure of hepatocarcinoma? A meta-analysis of propensity-matched and randomized studies for anatomic versus parenchyma-sparing liver resection. *J Gastrointest Surg*. 2021;25(1):94-103. doi:10.1007/s11605-019-04494-5
83. Moris D, Tsilimigras DI, Kostakis ID, et al. Anatomic versus non-anatomic resection for hepatocellular carcinoma: a systematic review and meta-analysis. *Eur J Surg Oncol*. 2018;44(7):927-938. doi:10.1016/j.ejso.2018.04.018
84. Shi M, Guo RP, Lin XJ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. *Ann Surg*. 2007;245(1):36-43. doi:10.1097/01.sla.0000231758.07868.71
85. Poon RT, Fan ST, Ng IO, Wong J. Significance of resection margin in hepatectomy for hepatocellular carcinoma: a critical reappraisal. *Ann Surg*. 2000;231(4):544-551. doi:10.1097/00000658-200004000-00014
86. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012;56(4):908-943. doi:10.1016/j.jhep.2011.12.001
87. Song TJ, Ip EWK, Fong Y. Hepatocellular carcinoma: current surgical management. *Gastroenterology*. 2004;127(5):S248-S260. doi:10.1053/j.gastro.2004.09.039
88. Moris D, Shaw BI, Ong C, et al. A simple scoring system to estimate perioperative mortality following liver resection for primary liver malignancy—the Hepatectomy Risk Score (HeRS). *Hepatobiliary Surg Nutr*. 2021;10(3):315-324. doi:10.21037/hbsn.2020.03.12
89. Citterio D, Facciorusso A, Sposito C, Rota R, Bhoori S, Mazzaferro V. Hierarchic interaction of factors associated with liver decompensation after resection for hepatocellular carcinoma. *JAMA Surg*. 2016;151(9):846-853. doi:10.1001/jamasurg.2016.1121
90. Maegawa FB, Shehorn L, Aziz H, Kettelle J, Jie T, Riall TS. Association between noninvasive fibrosis markers and postoperative mortality after hepatectomy for hepatocellular carcinoma. *JAMA Netw Open*. 2019;2(1):e187142. doi:10.1001/jamanetworkopen.2018.7142
91. Garcia-Pagan JC, Francoz C, Montagnese S, Senzolo M, Mookerjee RP. Management of the major complications of cirrhosis: beyond guidelines. *J Hepatol*. 2021;75(suppl 1):S135-S146. doi:10.1016/j.jhep.2021.01.027
92. Liang BY, Zhang EL, Li J, et al. A combined pre- and intra-operative nomogram in evaluation of degrees of liver cirrhosis predicts post-hepatectomy liver failure: a multicenter prospective study.

Hepatobiliary Surg Nutr. 2024;13(2):198-213. doi:10.21037/hbsn-22-410

93. Tsilimigras DI, Mehta R, Paredes AZ, et al. Overall tumor burden dictates outcomes for patients undergoing resection of multinodular hepatocellular carcinoma beyond the Milan criteria. *Ann Surg*. 2020;272(4):574-581. doi:10.1097/SLA.0000000000004346
94. Wei Z, Xie K, Xu F, Dai C. The tumor burden score may be a discriminator in microwave ablation versus liver resection for hepatocellular carcinoma within the Milan criteria: a propensity score matching and inverse probability of treatment weighting study. *Front Oncol*. 2024;14:1330851. doi:10.3389/fonc.2024.1330851
95. Ishizawa T, Hasegawa K, Aoki T, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology*. 2008;134(7):1908-1916. doi:10.1053/j.gastro.2008.02.091
96. Torzilli G, Belghiti J, Kokudo N, 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(5):929-937. doi:10.1097/SLA.0b013e31828329b8
97. Fukami Y, Kaneoka Y, Maeda A, et al. Liver resection for multiple hepatocellular carcinomas: a Japanese nationwide survey. *Ann Surg*. 2020;272(1):145-154. doi:10.1097/SLA.0000000000003192
98. Vitale A, Romano P, Cillo U, et al. Liver resection vs nonsurgical treatments for patients with early multinodular hepatocellular carcinoma. *JAMA Surg*. 2024;159(8):e241184. doi:10.1001/jamasurg.2024.1184
99. Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. *J Liver Cancer*. 2023;23(1):1-120. doi:10.17998/jlc.2022.11.07
100. Vitale A, Burra P, Frigo AC, et al. Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: a multicentre study. *J Hepatol*. 2015;62(3):617-624. doi:10.1016/j.jhep.2014.10.037
101. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. 2002;359(9319):1734-1739. doi:10.1016/S0140-6736(02)08649-X
102. Burrel M, Reig M, Forner A, et al. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using drug eluting beads. Implications for clinical practice and trial design. *J Hepatol*. 2012;56(6):1330-1335. doi:10.1016/j.jhep.2012.01.008
103. Dhanasekaran R, Kooby DA, Staley CA, Kauh JS, Khanna V, Kim HS. Prognostic factors for survival in patients with unresectable hepatocellular carcinoma undergoing chemoembolization with doxorubicin drug-eluting beads: a preliminary study. *HPB*. 2010;12(3):174-180. doi:10.1111/j.1477-2574.2009.00138.x
104. Takayasu K, Arii S, Ikai I, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. *Gastroenterology*. 2006;131(2):461-469. doi:10.1053/j.gastro.2006.05.021
105. Song MJ, Chun HJ, Song DS, et al. Comparative study between doxorubicin-eluting beads and conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. *J Hepatol*. 2012;57(6):1244-1250. doi:10.1016/j.jhep.2012.07.017
106. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334(11):693-699. doi:10.1056/NEJM199603143341104
107. Gores GJ. Liver transplantation for malignant disease. *Gastroenterol Clin North Am*. 1993;22(2):285-299. doi:10.1016/s0889-8553(21)00068-6
108. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. *Surgery*. 1991;110(4):726-734; discussion 734-735.
109. Mazzaferro V, Bhoori S, Sposito C, 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. doi:10.1002/lt.22365
110. 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(11):2587-2596. doi:10.1111/j.1600-6143.2007.01965.x
111. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology*. 2001;33(6):1394-1403. doi:10.1053/jhep.2001.24563
112. Agopian VG, Harlander-Locke MP, Ruiz RM, et al. Impact of pretransplant bridging locoregional therapy for patients with hepatocellular carcinoma within Milan criteria undergoing liver transplantation: analysis of 3601 patients from the US Multicenter HCC Transplant Consortium. *Ann Surg*. 2017;266(3):525-535. doi:10.1097/SLA.0000000000002381
113. Mohamed M, Katz AW, Tejani MA, et al. Comparison of outcomes between SBRT, yttrium-90 radioembolization, transarterial chemoembolization, and radiofrequency ablation as bridge to transplant for hepatocellular carcinoma. *Adv Radiat Oncol*. 2016;1(1):35-42. doi:10.1016/j.adro.2015.12.003
114. Mazzaferro V, Citterio D, Bhoori S, et al. Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): a randomised, controlled, phase 2b/3 trial. *Lancet Oncol*. 2020;21(7):947-956. doi:10.1016/S1470-2045(20)30224-2
115. Wassmer CH, El Hajji S, Papazarkadas X, et al. Immunotherapy and liver transplantation: a narrative review of basic and clinical data. *Cancers (Basel)*. 2023;15(18):4574. doi:10.3390/cancers15184574
116. Tabrizian P, Abdelrahim M, Schwartz M. Immunotherapy and transplantation for hepatocellular carcinoma. *J Hepatol*. 2024;80(5):822-825. doi:10.1016/j.jhep.2024.01.011
117. Washburn K, Edwards E, Harper A, Freeman R. Hepatocellular carcinoma patients are advantaged in the current liver transplant allocation system. *Am J Transplant*. 2010;10(7):1652-1657. doi:10.1111/j.1600-6143.2010.03127.x
118. Wong TCL, Ng KKC, Fung JYY, et al. Long-term survival outcome between living donor and deceased donor liver transplant for hepatocellular carcinoma: intention-to-treat and propensity score matching analyses. *Ann Surg Oncol*. 2019;26(5):1454-1462. doi:10.1245/s10434-019-07206-0
119. Azoulay D, Audureau E, Bhangui P, et al. Living or brain-dead donor liver transplantation for hepatocellular carcinoma: a multicenter, Western, intent-to-treat cohort study. *Ann Surg*. 2017;266(6):1035-1044. doi:10.1097/SLA.0000000000001986
120. Martinino A, Bucaro A, Cardella F, et al. Liver transplantation vs liver resection in HCC: promoting extensive collaborative research through a survival meta-analysis of meta-analyses. *Front Oncol*. 2024;14:1366607. doi:10.3389/fonc.2024.1366607
121. Wong LL, Landsittel DP, Kwee SA. Liver transplantation vs partial hepatectomy for stage T2 multifocal hepatocellular carcinoma <3 cm without vascular invasion: a propensity score-matched survival analysis. *J Am Coll Surg*. 2023;237(3):568-577. doi:10.1097/XCS.0000000000000725
122. Shah SA, Cleary SP, Wei AC, et al. Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. *Surgery*. 2007;141(3):330-339. doi:10.1016/j.surg.2006.06.028

123. Tsilimigras DI, Bagante F, Moris D, et al. Recurrence patterns and outcomes after resection of hepatocellular carcinoma within and beyond the Barcelona Clinic Liver Cancer criteria. *Ann Surg Oncol*. 2020;27(7):2321-2331. doi:10.1245/s10434-020-08452-3
124. Bruix J, Takayama T, Mazzaferro V, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2015;16(13):1344-1354. doi:10.1016/S1470-2045(15)00198-9
125. Yopp A, Kudo M, Chen M, et al. LBA39 Updated efficacy and safety data from IMbrave050: phase III study of adjuvant atezolizumab (atezo) + bevacizumab (bev) vs active surveillance in patients (pts) with resected or ablated high-risk hepatocellular carcinoma (HCC) [abstract]. *Ann Oncol*. 2024;35(suppl 2):S1230. doi:10.1016/j.annonc.2024.08.2279
126. Wei W, Jian PE, Li SH, et al. Adjuvant transcatheter arterial chemoembolization after curative resection for hepatocellular carcinoma patients with solitary tumor and microvascular invasion: a randomized clinical trial of efficacy and safety. *Cancer Commun*. 2018;38(1):61. doi:10.1186/s40880-018-0331-y
127. Sun J, Yang L, Shi J, et al. Postoperative adjuvant IMRT for patients with HCC and portal vein tumor thrombus: an open-label randomized controlled trial. *Radiother Oncol*. 2019;140:20-25. doi:10.1016/j.radonc.2019.05.006
128. Galle PR, Decaens T, Kudo M, et al. Nivolumab (NIVO) plus ipilimumab (IPI) vs lenvatinib (LEN) or sorafenib (SOR) as first-line treatment for unresectable hepatocellular carcinoma (uHCC): first results from CheckMate 9DW [abstract]. *J Clin Oncol*. 2024;42(17 suppl):LBA4008. doi:10.1200/JCO.2024.42.17_suppl.LBA4008
129. Knox J, Cheng A, Cleary S, et al. P-217—A phase 3 study of durvalumab with or without bevacizumab as adjuvant therapy in patients with hepatocellular carcinoma at high risk of recurrence after curative hepatic resection or ablation: EMERALD-2 [abstract]. *Ann Oncol*. 2019;30:iv59-iv60. doi:10.1093/annonc/mdz155.216
130. Goyal L, Vogel A, Zhu AX, et al. P024 KEYNOTE-937 trial in progress: adjuvant pembrolizumab for hepatocellular carcinoma and complete radiologic response after surgical resection or local ablation [abstract]. *Gut*. 2021;70(suppl 3):A22. doi:10.1136/gutjnl-2021-BASL.33
131. Bruix J, Llovet HM, Castells A, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. *Hepatology*. 1998;27(6):1578-1583. doi:10.1002/hep.510270617
132. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology*. 2002;35(5):1164-1171. doi:10.1053/jhep.2002.33156
133. Varela M, Real MI, Burrel M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol*. 2007;46(3):474-481. doi:10.1016/j.jhep.2006.10.020
134. Lammer J, Malagari K, Vogl T, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Interv Radiol*. 2010;33(1):41-52. doi:10.1007/s00270-009-9711-7
135. Golfieri R, Giampalma E, Renzulli M, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. *Br J Cancer*. 2014;111(2):255-264. doi:10.1038/bjc.2014.199
136. Zou JH, Zhang L, Ren ZG, Ye SL. Efficacy and safety of cTACE versus DEB-TACE in patients with hepatocellular carcinoma: a meta-analysis. *J Dig Dis*. 2016;17(8):510-517. doi:10.1111/1751-2980.12380
137. Wang H, Cao C, Wei X, et al. A comparison between drug-eluting bead-transarterial chemoembolization and conventional transarterial chemoembolization in patients with hepatocellular carcinoma: a meta-analysis of six randomized controlled trials. *J Cancer Res Ther*. 2020;16(2):243-249. doi:10.4103/jcrt.JCRT_504_19
138. Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma—a randomized controlled trial. *Gastroenterology*. 1988;94(2):453-456. doi:10.1016/0016-5085(88)90436-2
139. Pelletier G, Roche A, Ink O, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. *J Hepatol*. 1990;11(2):181-184. doi:10.1016/0168-8278(90)90110-D
140. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med*. 1995;332(19):1256-1261. doi:10.1056/nejm199505113321903
141. Pelletier G, Ducreux M, Gay F, et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. *J Hepatol*. 1998;29(1):129-134. doi:10.1016/S0168-8278(98)80187-6
142. Marelli L, Stigliano R, Triantos C, et al. Transarterial therapy for hepatocellular carcinoma: which technique is more effective? A systematic review of cohort and randomized studies. *Cardiovasc Interv Radiol*. 2007;30(1):6-25. doi:10.1007/s00270-006-0062-3
143. Lanza E, Donadon M, Poretti D, et al. Transarterial therapies for hepatocellular carcinoma. *Liver Cancer*. 2016;6(1):27-33. doi:10.1159/000449347
144. Brown KT, Do RK, Gonen M, et al. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. *J Clin Oncol*. 2016;34(17):2046-2053. doi:10.1200/JCO.2015.64.0821
145. Briody H, Duong D, Yeoh SW, et al. Radioembolization for treatment of hepatocellular carcinoma: current evidence and patterns of utilization. *J Vasc Interv Radiol*. 2023;34(7):1200-1213. doi:10.1016/j.jvir.2023.03.020
146. Mikell JK, Dewaraja YK, Owen D. Transarterial radioembolization for hepatocellular carcinoma and hepatic metastases: clinical aspects and dosimetry models. *Semin Radiat Oncol*. 2020;30(1):68-76. doi:10.1016/j.semradonc.2019.08.005
147. Fidelman N, Kerlan RK. Transarterial chemoembolization and (90)Y radioembolization for hepatocellular carcinoma: review of current applications beyond intermediate-stage disease. *AJR Am J Roentgenol*. 2015;205(4):742-752. doi:10.2214/AJR.15.14802
148. Vouche M, Lewandowski RJ, Atassi R, et al. Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. *J Hepatol*. 2013;59(5):1029-1036. doi:10.1016/j.jhep.2013.06.015
149. Riaz A, Gates VL, Atassi B, et al. Radiation segmentectomy: a novel approach to increase safety and efficacy of radioembolization. *Int J Radiat Oncol Biol Phys*. 2011;79(1):163-171. doi:10.1016/j.ijrobp.2009.10.062
150. Lewandowski RJ, Gabr A, Abouchaleh N, et al. Radiation segmentectomy: potential curative therapy for early hepatocellular carcinoma. *Radiology*. 2018;287(3):1050-1058. doi:10.1148/radiol.2018171768
151. Cardarelli-Leite L, Chung J, Klass D, et al. Ablative transarterial radioembolization improves survival in patients with HCC and portal vein tumor thrombus. *Cardiovasc Interv Radiol*. 2020;43(3):411-422. doi:10.1007/s00270-019-02404-5
152. Meerun MA, Allimant C, Rivière B, et al. Large, multifocal or portal vein-invading hepatocellular carcinoma (HCC) downstaged by Y90 using personalized dosimetry: safety, pathological results and

outcomes after surgery. *Hepatobiliary Surg Nutr*. 2023;12(3):351-365. doi:10.21037/hbsn-22-184
153. Allimant C, Kafrouni M, Delicque J, et al. Tumor targeting and three-dimensional voxel-based dosimetry to predict tumor response, toxicity, and survival after yttrium-90 resin microsphere radioembolization in hepatocellular carcinoma. *J Vasc Interv Radiol*. 2018;29(12):1662-1670.e4. doi:10.1016/j.jvir.2018.07.006
154. Garin E, Tselikas L, Guiu B, et al. Personalised versus standard dosimetry approach of selective internal radiation therapy in patients with locally advanced hepatocellular carcinoma (DOSISPHERE-01): a randomised, multicentre, open-label phase 2 trial. *Lancet Gastroenterol Hepatol*. 2021;6(1):17-29. doi:10.1016/S2468-1253(20)30290-9
155. Garin E, Tselikas L, Guiu B, et al. Long-term overall survival after selective internal radiation therapy for locally advanced hepatocellular carcinomas: updated analysis of DOSISPHERE-01 trial. *J Nucl Med*. 2024;65(2):264-269. doi:10.2967/jnumed.123.266211
156. Badar W, Yu Q, Patel M, Ahmed O. Transarterial radioembolization for management of hepatocellular carcinoma. *Oncologist*. 2024;29(2):117-122. doi:10.1093/oncolo/oyad327
157. Salem R, Gordon AC, Mouli S, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology*. 2016;151(6):1155-1163.e2. doi:10.1053/j.gastro.2016.08.029
158. Dhondt E, Lambert B, Hermie L, et al. 90Y radioembolization versus drug-eluting bead chemoembolization for unresectable hepatocellular carcinoma: results from the TRACE phase II randomized controlled trial. *Radiology*. 2022;303(3):699-710. doi:10.1148/radiol.211806
159. Salem R, Johnson GE, Kim E, et al. Yttrium-90 radioembolization for the treatment of solitary, unresectable HCC: the LEGACY study. *Hepatology*. 2021;74(5):2342-2352. doi:10.1002/hep.31819
160. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol*. 2017;18(12):1624-1636. doi:10.1016/S1470-2045(17)30683-6
161. Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Orthod*. 2018;36(19):1913-1921. doi:10.1200/JCO.2017.76.0892
162. Sharib JM, Creasy JM, Wildman-Tobriner B, et al. Hepatic artery infusion pumps: a surgical toolkit for intraoperative decision-making and management of hepatic artery infusion-specific complications. *Ann Surg*. 2022;276(6):943-956. doi:10.1097/SLA.0000000000005434
163. Anteby R, Kemeny NE, Kingham TP, et al. Getting chemotherapy directly to the liver: the historical evolution of hepatic artery chemotherapy. *J Am Coll Surg*. 2021;232(3):332-338. doi:10.1016/j.jamcollsurg.2020.11.013
164. Kemeny NE, Niedzwiecki D, Hollis DR, et al. Hepatic arterial infusion versus systemic therapy for hepatic metastases from colorectal cancer: a randomized trial of efficacy, quality of life, and molecular markers (CALGB 9481). *J Clin Oncol*. 2006;24(9):1395-1403. doi:10.1200/JCO.2005.03.8166
165. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med*. 1999;341(27):2039-2048. doi:10.1056/NEJM199912303412702
166. Cercek A, Boerner T, Tan BR, et al. Assessment of hepatic arterial infusion of floxuridine in combination with systemic gemcitabine and oxaliplatin in patients with unresectable intrahepatic cholangiocarcinoma: a phase 2 clinical trial. *JAMA Oncol*. 2020;6(1):60-67. doi:10.1001/jamaoncol.2019.3718
167. Moris D, Palta M, Kim C, Allen PJ, Morse MA, Lidsky ME. Advances in the treatment of intrahepatic cholangiocarcinoma: an overview of the current and future therapeutic landscape for clinicians. *CA Cancer J Clin*. 2023;73(2):198-222. doi:10.3322/caac.21759
168. Lyu N, Wang X, Li JB, et al. Arterial chemotherapy of oxaliplatin plus fluorouracil versus sorafenib in advanced hepatocellular carcinoma: a biomolecular exploratory, randomized, phase III trial (FOHAIC-1). *J Clin Oncol*. 2022;40(5):468-480. doi:10.1200/JCO.21.01963
169. He M, Li Q, Zou R, et al. Sorafenib plus hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin vs sorafenib alone for hepatocellular carcinoma with portal vein invasion: a randomized clinical trial. *JAMA Oncol*. 2019;5(7):953-960. doi:10.1001/jamaoncol.2019.0250
170. Li QJ, He MK, Chen HW, et al. Hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin versus transarterial chemoembolization for large hepatocellular carcinoma: a randomized phase III trial. *J Clin Oncol*. 2022;40(2):150-160. doi:10.1200/JCO.21.00608
171. Si T, Huang Z, Khorsandi SE, Ma Y, Heaton N. Hepatic arterial infusion chemotherapy versus transarterial chemoembolization for unresectable hepatocellular carcinoma: a systematic review with meta-analysis. *Front Bioeng Biotechnol*. 2022;10:1010824. doi:10.3389/fbioe.2022.1010824
172. Nault JC, Sutter O, Nahon P, Ganne-Carrié N, Séror O. Percutaneous treatment of hepatocellular carcinoma: state of the art and innovations. *J Hepatol*. 2018;68(4):783-797. doi:10.1016/j.jhep.2017.10.004
173. Poulou LS, Botsa E, Thanou I, Ziakas PD, Thanos L. Percutaneous microwave ablation vs radiofrequency ablation in the treatment of hepatocellular carcinoma. *World J Hepatol*. 2015;7(8):1054-1063. doi:10.4254/wjh.v7.i8.1054
174. Groeschl RT, Pilgrim CHC, Hanna EM, et al. Microwave ablation for hepatic malignancies: a multiinstitutional analysis. *Ann Surg*. 2014;259(6):1195-1200. doi:10.1097/SLA.0000000000000234
175. Huang J, Yan L, Cheng Z, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg*. 2010;252(6):903-912. doi:10.1097/SLA.0b013e3181efc656
176. Feng K, Yan J, Li X, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. *J Hepatol*. 2012;57(4):794-802. doi:10.1016/j.jhep.2012.05.007
177. Ng KKC, Chok KSH, Chan ACY, et al. Randomized clinical trial of hepatic resection versus radiofrequency ablation for early-stage hepatocellular carcinoma. *Br J Surg*. 2017;104(13):1775-1784. doi:10.1002/bjs.10677
178. Takayama T, Hasegawa K, Izumi N. Surgery versus radiofrequency ablation for small hepatocellular carcinoma. a randomized controlled trial (SURF Trial). *Liver Cancer*. 2021;29(11):209-218. doi:10.1159/000521665
179. Rossi S, Di Stasi M, Buscarini E, et al. Percutaneous radiofrequency interstitial thermal ablation in the treatment of small hepatocellular carcinoma. *Cancer J Sci Am*. 1995;1(1):73-81.
180. Kudo M, Osaki Y, Matsunaga T, Kasugai H, Oka H, Seki T. Hepatocellular carcinoma in Child–Pugh C cirrhosis: prognostic factors and survival benefit of nontransplant treatments. *Dig Dis*. 2013;31(5-6):490-498. doi:10.1159/000355259
181. Huo YR, Eslick GD. Microwave ablation compared to radiofrequency ablation for hepatic lesions: a meta-analysis. *J Vasc Interv Radiol*. 2015;26(8):1139-1146.e2. doi:10.1016/j.jvir.2015.04.004
182. Han B, Li C, Meng H, et al. Efficacy and safety of external-beam radiation therapy for hepatocellular carcinoma: an overview of current evidence according to the different target population. *Biosci Trends*. 2019;13(1):10-22. doi:10.5582/bst.2018.01261

183. Apisarnthanarax S, Barry A, Cao M, et al. External beam radiation therapy for primary liver cancers: an ASTRO clinical practice guideline. *Pract Radiat Oncol*. 2022;12(1):28-51. doi:10.1016/j.prro.2021.09.004
184. Chino F, Stephens SJ, Choi SS, et al. The role of external beam radiotherapy in the treatment of hepatocellular cancer. *Cancer*. 2018;124(17):3476-3489. doi:10.1002/cncr.31334
185. Yang D, Lin K, Wang Y, Xie X, Xie X, Zhuang B. Stereotactic body radiation therapy versus radiofrequency ablation in hepatocellular carcinoma: an up-date meta-analysis. *Abdom Radiol (NY)*. 2023;48(1):399-410. doi:10.1007/s00261-022-03690-3
186. xWahl DR, Stenmark MH, Tao Y, et al. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol*. 2016;34(5):452-459. doi:10.1200/JCO.2015.61.4925
187. Weiner AA, Olsen J, Ma D, et al. Stereotactic body radiotherapy for primary hepatic malignancies—report of a phase I/II institutional study. *Radiother Oncol*. 2016;121(1):79-85. doi:10.1016/j.radonc.2016.07.020
188. Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol*. 2013;31(13):1631-1639. doi:10.1200/JCO.2012.44.1659
189. Lasley FD, Mannina EM, Johnson CS, et al. Treatment variables related to liver toxicity in patients with hepatocellular carcinoma, Child–Pugh class A and B enrolled in a phase 1–2 trial of stereotactic body radiation therapy. *Pract Radiat Oncol*. 2015;5(5):e443-e449. doi:10.1016/j.prro.2015.02.007
190. Soni PD, Palta M. Stereotactic body radiation therapy for hepatocellular carcinoma: current state and future opportunities. *Dig Dis Sci*. 2019;64(4):1008-1015. doi:10.1007/s10620-019-05539-0
191. Sapisochin G, Barry A, Doherty M, et al. Stereotactic body radiotherapy vs. TACE or RFA as a bridge to transplant in patients with hepatocellular carcinoma. An intention-to-treat analysis. *J Hepatol*. 2017;67(1):92-99. doi:10.1016/j.jhep.2017.02.022
192. Vernuccio F, Godfrey D, Meyer M, et al. Local tumor control and patient outcome using stereotactic body radiation therapy for hepatocellular carcinoma: iRECIST as a potential substitute for traditional criteria. *AJR Am J Roentgenol*. 2019;213(6):1232-1239. doi:10.2214/AJR.18.20842
193. Wigg A, Tibballs J, Woodman R, et al. A randomised controlled trial of Standard Of Care versus RadioAblaTion in Early Stage HepatoCellular Carcinoma (SOCRATES HCC). *BMC Cancer*. 2024;24(1):813. doi:10.1186/s12885-024-12504-2
194. Dawson LA, Winter KA, Knox JJ, et al. NRG/RTOG 1112: randomized phase III study of sorafenib vs. stereotactic body radiation therapy (SBRT) followed by sorafenib in hepatocellular carcinoma (HCC) [abstract]. *J Clin Orthod*. 2023;41(4 suppl):489. doi:10.1200/JCO.2023.41.4_suppl.489
195. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol*. 2022;76(4):862-873. doi:10.1016/j.jhep.2021.11.030
196. Qin S, Chan SL, Gu S, 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(10408):1133-1146. doi:10.1016/S0140-6736(23)00961-3
197. Ren Z, Xu J, Bai Y, 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(7):977-990. doi:10.1016/S1470-2045(21)00252-7
198. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evid*. 2022;1(8):EVIDoa2100070. doi:10.1056/EVIDoa2100070
199. Kelley RK, Rimassa L, Cheng AL, et al. Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2022;23(8):995-1008. doi:10.1016/S1470-2045(22)00326-6
200. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008;359(4):378-390. doi:10.1056/NEJMoa0708857
201. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018;391(10126):1163-1173. doi:10.1016/S0140-6736(18)30207-1
202. Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol*. 2022;23(1):77-90. doi:10.1016/S1470-2045(21)00604-5
203. Qin S, Kudo M, Meyer T, et al. Tislelizumab vs sorafenib as first-line treatment for unresectable hepatocellular carcinoma: a phase 3 randomized clinical trial. *JAMA Oncol*. 2023;9(12):1651-1659. doi:10.1001/jamaoncol.2023.4003
204. Peng Z, Fan W, Zhu B, 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(1):117-127. doi:10.1200/JCO.22.00392
205. Roessler D, Öcal O, Philipp AB, et al. Ipilimumab and nivolumab in advanced hepatocellular carcinoma after failure of prior immune checkpoint inhibitor-based combination therapies: a multicenter retrospective study. *J Cancer Res Clin Oncol*. 2023;149(7):3065-3073. doi:10.1007/s00432-022-04206-8
206. Alden SL, Lim M, Kao C, et al. Salvage ipilimumab plus nivolumab after anti-PD-1/PD-L1 therapy in advanced hepatocellular carcinoma. *Cancer Res Commun*. 2023;3(7):1312-1317. doi:10.1158/2767-9764.CRC-23-0072
207. Kim HJ, Hwang SY, Im JW, Jeon KJ, Jeon W. A case of nearly complete response in hepatocellular carcinoma with disseminated lung metastasis by combination therapy of nivolumab and ipilimumab after treatment failure of atezolizumab plus bevacizumab. *J Liver Cancer*. 2023;23(1):213-218. doi:10.17998/jlc.2023.02.23
208. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10064):56-66. doi:10.1016/S0140-6736(16)32453-9
209. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. *N Engl J Med*. 2018;379(1):54-63. doi:10.1056/NEJMoa1717002
210. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2019;20(2):282-296. doi:10.1016/S1470-2045(18)30937-9
211. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab as second-line therapy in patients with advanced hepatocellular carcinoma in KEYNOTE-240: a randomized, double-blind, phase III trial. *J Clin Oncol*. 2020;38(3):193-202. doi:10.1200/JCO.19.01307
212. Qin S, Chen Z, Fang W, et al. Pembrolizumab versus placebo as second-line therapy in patients from Asia with advanced hepatocellular carcinoma: a randomized, double-blind, phase III trial. *J Clin Oncol*. 2023;41(7):1434-1443. doi:10.1200/JCO.22.00620
213. Qin S, Li Q, Gu S, et al. Apatinib as second-line or later therapy in patients with advanced hepatocellular carcinoma (AHELP): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol*. 2021;6(7):559-568. doi:10.1016/S2468-1253(21)00109-6

214. Finn RS, Yau T, Hsu CH, et al. Ramucirumab for patients with advanced hepatocellular carcinoma and elevated alpha fetoprotein following non–sorafenib systemic therapy: an expansion cohort of REACH-2. *Oncologist*. 2022;27(12):e938-e948. doi:10.1093/oncolo/oyac183
215. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell*. 2015;27(4):450-461. doi:10.1016/j.ccell.2015.03.001
216. Gordan JD, Kennedy EB, Abou-Alfa GK, et al. Systemic therapy for advanced hepatocellular carcinoma: ASCO guideline update. *J Clin Oncol*. 2024;42(15):1830-1850. doi:10.1200/JCO.23.02745
217. Moris D, Rahnemai-Azar AA, Zhang X, et al. Program death-1 immune checkpoint and tumor microenvironment in malignant liver tumors. *Surg Oncol*. 2017;26(4):423-430. doi:10.1016/j.suronc.2017.08.005
218. Yau T, Kang YK, Kim TY, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. *JAMA Oncol*. 2020;6(11):e204564. doi:10.1001/jamaoncol.2020.4564
219. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020;382(20):1894-1905. doi:10.1056/NEJMoa1915745
220. Sangro B, Chan SL, Kelley RK, et al. Four-year overall survival update from the phase III HIMALAYA study of tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *Ann Oncol*. 2024;35(5):448-457. doi:10.1016/j.annonc.2024.02.005
221. Vogel A, Chan SL, Ren Z, et al. Camrelizumab plus rivoceranib vs sorafenib as first-line therapy for unresectable hepatocellular carcinoma (uHCC): final overall survival analysis of the phase 3 CARES-310 study [abstract]. *J Clin Orthod*. 2024;42(16 suppl):4110. doi:10.1200/JCO.2024.42.16_suppl.4110
222. Verset G, Borbath I, Karwal M, et al. Pembrolizumab monotherapy for previously untreated advanced hepatocellular carcinoma: data from the open-label, phase II KEYNOTE-224 trial. *Clin Cancer Res*. 2022;28(12):2547-2554. doi:10.1158/1078-0432.CCR-21-3807
223. Lencioni R, Kudo M, Erinjeri J, et al. EMERALD-1: phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization [abstract]. *J Clin Oncol*. 2024;42(3 suppl):LBA432. doi:10.1200/jco.2024.42.3_suppl.LBA432
224. Llovet J, Finn RS, Ren Z, et al. LBA3 Transarterial chemoembolization (TACE) with or without lenvatinib (len) + pembrolizumab (pembro) for intermediate-stage hepatocellular carcinoma (HCC): phase III LEAP-012 study [abstract]. *Ann Oncol*. 2024;35:S1229. doi:10.1016/j.annonc.2024.08.2277
225. Lee YB, Nam JY, Cho EJ, et al. A phase I/IIa trial of yttrium-90 radioembolization in combination with durvalumab for locally advanced unresectable hepatocellular carcinoma. *Clin Cancer Res*. 2023;29(18):3650-3658. doi:10.1158/1078-0432.CCR-23-0581
226. Yu S, Yu M, Keane B, et al. A pilot study of pembrolizumab in combination with Y90 radioembolization in subjects with poor prognosis hepatocellular carcinoma. *Oncologist*. 2024;29(3):270-e413-e413. doi:10.1093/oncolo/oyad331
227. Kaya NA, Tai D, Lim X, et al. Multimodal molecular landscape of response to Y90-resin microsphere radioembolization followed by nivolumab for advanced hepatocellular carcinoma. *J Immunother Cancer*. 2023;11(8):e007106. doi:10.1136/jitc-2023-007106
228. Hui S, Sane N, Wang A, et al. Hepatocellular carcinoma surveillance in the telehealth era: a single-centre review. *J Telemed Telecare*. 2025;31(1):64-72. doi:10.1177/1357633X231166032
229. Choi DT, Sada YH, Sansgiry S, et al. Using telemedicine to facilitate patient communication and treatment decision-making following multidisciplinary tumor board review for patients with hepatocellular carcinoma. *J Gastrointest Cancer*. 2023;54(2):623-631. doi:10.1007/s12029-022-00844-w
230. Murali M, Kumar AR, Nair B, et al. Antibody-drug conjugate as targeted therapeutics against hepatocellular carcinoma: preclinical studies and clinical relevance. *Clin Transl Oncol*. 2022;24(3):407-431. doi:10.1007/s12094-021-02707-5
231. Zhou Y, Wei S, Xu M, et al. CAR-T cell therapy for hepatocellular carcinoma: current trends and challenges. *Front Immunol*. 2024;15:1489649. doi:10.3389/fimmu.2024.1489649
232. Aggeletopoulou I, Kalafateli M, Triantos C. Chimeric antigen receptor T cell therapy for hepatocellular carcinoma: where do we stand? *Int J Mol Sci*. 2024;25(5):2631. doi:10.3390/ijms25052631
233. Cheung TTT, Kwok PCH, Chan S, et al. Hong Kong consensus statements for the management of unresectable hepatocellular carcinoma. *Liver Cancer*. 2018;7(1):40-54. doi:10.1159/000485984
234. Yen YH, Kee KM, Li WF, et al. Causes of death among patients with hepatocellular carcinoma according to chronic liver disease etiology. *Cancers (Basel)*. 2023;15(6):1687. doi:10.3390/cancers15061687
235. Agarwal PD, Phillips P, Hillman L, et al. Multidisciplinary management of hepatocellular carcinoma improves access to therapy and patient survival. *J Clin Gastroenterol*. 2017;51(9):845-849. doi:10.1097/MCG.0000000000000825
236. Yopp AC, Mansour JC, Beg MS, et al. Establishment of a multidisciplinary hepatocellular carcinoma clinic is associated with improved clinical outcome. *Ann Surg Oncol*. 2014;21(4):1287-1295. doi:10.1245/s10434-013-3413-8
237. Gaba RC, Kallwitz ER, Parvinian A, et al. Imaging surveillance and multidisciplinary review improves curative therapy access and survival in HCC patients. *Ann Hepatol*. 2013;12(5):766-773. doi:10.1016/s1665-2681(19)31318-3

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Moris D, Martinino A, Schiltz S, et al. Advances in the treatment of hepatocellular carcinoma: an overview of the current and evolving therapeutic landscape for clinicians. *CA Cancer J Clin*. 2025;75(6):498-527. doi:10.3322/caac.70018