REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

# Hepatocellular Carcinoma

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Hepatocellular carcinoma accounts for the majority of primary liver cancers. Worldwide, liver cancers are the fourth most common cause of cancer-related death and rank sixth in terms of incident cases (Fig. 1).[1] On the basis of annual projections, the World Health Organization estimates that more than 1 million patients will die from liver cancer in 2030.[2] In the United States, the rate of death from liver cancer increased by 43% (from 7.2 to 10.3 deaths per 100,000) between 2000 and 2016.[3] With a 5-year survival of 18%, liver cancer is the second most lethal tumor, after pancreatic cancer.[4] The majority of hepatocellular carcinomas occur in patients with underlying liver disease, mostly as a result of hepatitis B or C virus (HBV or HCV) infection or alcohol abuse. Universal HBV vaccination and wide implementation of direct-acting antiviral agents against HCV are likely to change the etiologic landscape of hepatocellular carcinoma. However, the increase in nonalcoholic fatty liver disease (NAFLD), which together with metabolic syndrome and obesity amplifies the risk of liver cancer, will soon become a leading cause of liver cancer in Western countries.[5] Racial or ethnic group differences play an important role in the probability of survival, with blacks and Hispanics less likely than whites to undergo curative therapies.[6] Systemic therapies for patients with an advanced stage of liver cancer are rapidly changing, with four new agents showing clinical efficacy in phase 3 trials in the past 2 years.[7] This review summarizes the main genetic alterations in hepatocellular carcinoma, key epidemiologic features, and evidence-based approaches to management.

## Molecular Pathogenesis

Patients with chronic liver disease have sustained hepatic inflammation, fibrosis, and aberrant hepatocyte regeneration. These abnormalities can cause cirrhosis and favor a series of genetic and epigenetic events that culminate in the formation of dysplastic nodules, which are bona fide preneoplastic lesions. Additional molecular alterations provide dysplastic cells with proliferative, invasive, and survival advantages and complete the transition to full-blown hepatocellular carcinoma (Fig. 2).[8] Hepatocellular carcinoma can also arise in patients who have chronic liver disease but do not have established cirrhosis or marked inflammation (e.g., patients with HBV infection).

### Genetic Alterations

Hepatocellular carcinoma cells accumulate somatic DNA alterations, including mutations and chromosomal aberrations. Mutations in the *TERT* promoter are the most frequent genetic alterations, accounting for approximately 60% of cases.[9] They can be detected in dysplastic nodules, and the *TERT* promoter is a recurrent insertion site for the genome of HBV. Oncogenic viral insertions of adeno-associated virus type 2 in the *TERT* promoter have also been reported, but their preva-

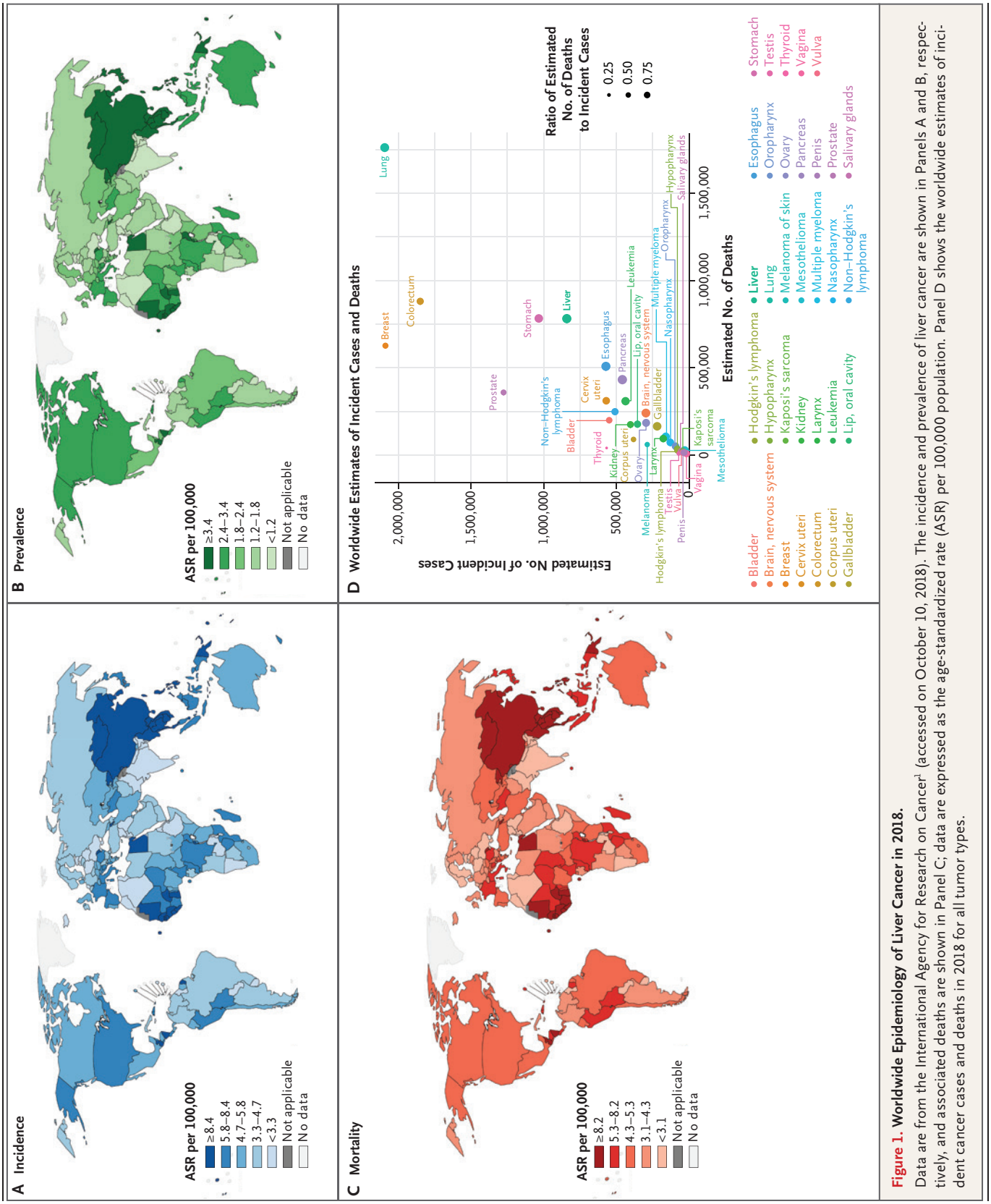


**Figure 1. Worldwide Epidemiology of Liver Cancer in 2018.**

Data are from the International Agency for Research on Cancer[1] (accessed on October 10, 2018). The incidence and prevalence of liver cancer are shown in Panels A and B, respectively, and associated deaths are shown in Panel C; data are expressed as the age-standardized rate (ASR) per 100,000 population. Panel D shows the worldwide estimates of incident cancer cases and deaths in 2018 for all tumor types.

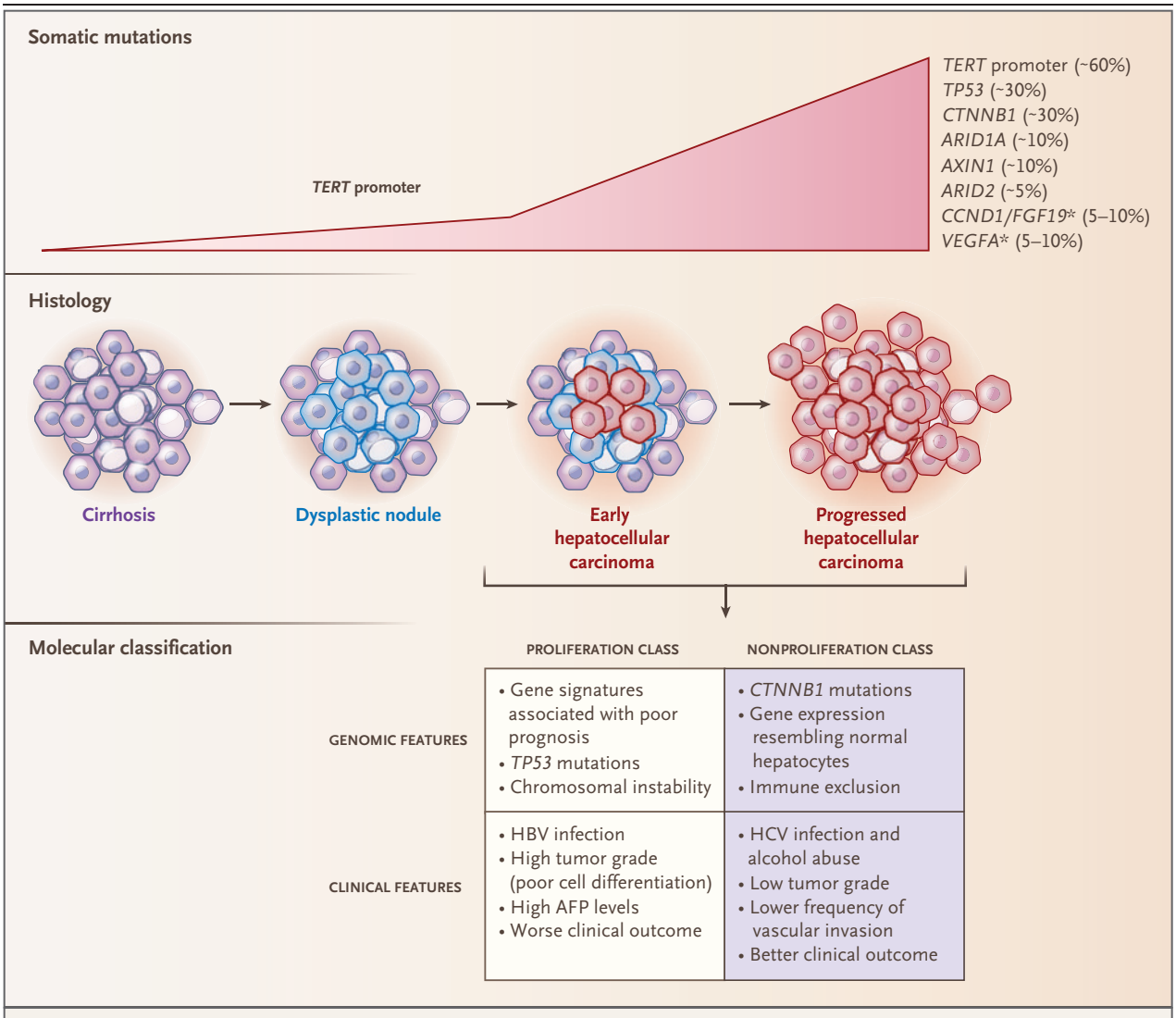


**Figure 2. Main Genetic Alterations in Hepatocellular Carcinoma and Molecular Classification.**

The key molecular and histologic alterations occurring during human hepatocarcinogenesis are summarized, as are the main genomic and clinical features of the two main molecular subclasses of hepatocellular carcinoma. An asterisk (*) denotes high-level DNA amplification. In the nonproliferation class, immune exclusion is enriched in tumors with *CTNNB1* mutations. AFP denotes alpha-fetoprotein, HBV hepatitis B virus, and HCV hepatitis C virus.

lence is very low (approximately 5%).[9] Other mutated genes affect the cell cycle (e.g., *TP53*, accounting for approximately 30% of cases), WNT signaling (*CTNNB1* and *AXIN1*, accounting for approximately 30% and 10% of cases, respectively), or chromatin remodeling (*ARID1A* and *ARID2*, accounting for approximately 10% and 5% of cases, respectively) (Fig. 2). Hepatocellular carcinoma is among the solid cancers with the fewest somatic mutations that can be targeted with molecular therapies,[10] and no mutation is used in clinical practice to predict a therapeutic response. High-level DNA amplifications located in chromosome 6p21 and 11q13, the respective loci for *VEGFA* and *CCND1*/*FGF19*, could also be targeted with molecular therapies, but their prevalence is low.

### MOLECULAR CLASSIFICATION AND BIOMARKERS

Patients with hepatocellular carcinoma at the same clinical stage can have different molecular subtypes. These subtypes correlate with clinical

features, but they are not used in routine clinical practice. They were identified on the basis of specimens resected from patients at early disease stages but have not been thoroughly tested as predictors of a response to systemic therapies, which has limited their clinical usefulness. The molecular subtypes can be grouped in two main classes: the proliferation class and the nonproliferation class (Fig. 2).[11] The proliferation class, more commonly seen in patients with HBV infection, is characterized by molecular and histologic features that result in aggressive clinical behavior, including high serum levels of alpha-fetoprotein, poor cell differentiation, chromosomal instability, *TP53* mutations, and activation of oncogenic pathways (e.g., RAS–mitogen-activated protein kinase [MAPK], AKT–mammalian target of rapamycin [mTOR], and MET [a hepatocyte growth factor receptor]). Most of the gene signatures associated with a poor clinical outcome are also enriched in the proliferation class.[12] Tumors of the nonproliferation class have more *CTNNB1* (beta-catenin) mutations, and their gene-expression pattern resembles that of normal hepatocytes.

Hepatocellular carcinomas are complex ecosystems incorporating nontumor cells, mainly immune-related cells. The success of immune checkpoint inhibition in solid tumors underscores the key role of the tumor microenvironment in the progression of cancer. Approximately 30% of early-stage hepatocellular carcinomas have genomic evidence of immune activation,[13] whereas 25% have no immune infiltrate. Understanding the interaction between cancer cells and their microenvironment will be crucial for developing new therapies and identifying biomarkers.

## RISK FACTORS

Hepatocellular carcinoma is rare among patients without liver disease and is twice as common in men as in women. Cirrhosis of any cause increases the risk of hepatocellular carcinoma, with an annual incidence between 2 and 4%. This risk varies according to cause, geographic area, sex, age, and degree of liver damage.[14] Worldwide, HBV infection is the main cause of hepatocellular carcinoma. Although HBV vaccination reduces the incidence of hepatocellular carcinoma,[15] many unvaccinated persons are still infected with HBV (257 million in 2015) and thus at risk for hepatocellular carcinoma, mostly in Asia and sub-Saharan Africa.[16] Dietary exposure to aflatoxin B1 amplifies the risk of hepatocellular carcinoma among patients with HBV infection, through a specific mutation in *TP53* at position 249 (R→S). In Western countries and Japan, the main cause of hepatocellular carcinoma is HCV infection. HBV infection has a direct oncogenic effect, regardless of the degree of underlying liver fibrosis,[17] but hepatocellular carcinoma rarely occurs in HCV-infected patients who do not have advanced fibrosis. The incidence of hepatocellular carcinoma due to NAFLD is increasing worldwide. In the United States, the incidence is expected to increase by 122% between 2016 and 2030, from 5510 to 12,240 cases.[18] Alcoholic cirrhosis is another frequent cause of hepatocellular carcinoma. Smoking and coinfection with the human immunodeficiency virus can also contribute to the development of hepatocellular carcinoma.

Antiviral therapies are effective in reducing the incidence of hepatocellular carcinoma but do not eradicate the risk.[19] Among patients with HCV infection who have a sustained virologic response to interferon-based treatment regimens, the risk of hepatocellular carcinoma is reduced from 6.2 to 1.5%, as compared with patients who do not have a response.[20] Reduction in the risk of hepatocellular carcinoma has been reported among HCV-infected patients treated with direct-acting antiviral agents.[21] Such patients typically have more advanced fibrosis than those who received interferon-based therapies.[22] Apart from treatment of the cause of the liver disease, no drugs are known to reduce the incidence of hepatocellular carcinoma.

## SURVEILLANCE

Cancer surveillance aims to detect tumors at early stages, increase the opportunity to use curative treatments, and improve survival. However, no high-quality randomized, controlled trials have evaluated the effect of hepatocellular carcinoma surveillance in patients with cirrhosis. One study underscored the difficulties of conducting such a trial, with 99% of patients declining to assume the risk of being randomly assigned to the nonsurveillance group.[23] Nonetheless, mathematical models,[24] a low-quality

clinical trial (with methodologic limitations),[25] and more important, a meta-analysis of cohort studies[26] all show survival benefits of surveillance. This evidence substantiates the recommendation of surveillance by major hepatology professional societies.[27-29] Recent criticisms of surveillance include a small net benefit with increased harms as a result of false positive results[30] and lack of a decrease in disease-specific mortality,[31] on the basis of nonrandomized studies. The target population for surveillance is patients with cirrhosis, regardless of the cause. The annual incidence of hepatocellular carcinoma among these patients surpasses the threshold of 1.5% that renders surveillance cost-effective.[32] Patients with cirrhosis and advanced liver dysfunction, who would not be eligible for a curative treatment, are not candidates for surveillance. This does not apply to candidates for liver transplantation as a result of liver dysfunction. The goal of surveillance for patients on the transplant waiting list is to ensure that a tumor does not develop that would preclude transplantation according to established criteria.

Some patients who have liver disease without cirrhosis should also be enrolled in surveillance programs. The risk of hepatocellular carcinoma among patients with chronic HBV infection varies across geographic regions (with higher risks in Africa and Asia than in other regions) and increases with age, male sex, presence of liver fibrosis, high level of viral replication, genotype C, and a family history of hepatocellular carcinoma.[33] Various scoring systems are available to quantify this risk, but none are universally accepted because of suboptimal validation across geographic regions.[34] Patients with chronic HCV infection and advanced fibrosis, defined by the Metavir system as a score of F3 or higher on a scale of F0 to F4, with higher scores indicating more severe fibrosis (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org),[35] are at sufficient risk to undergo surveillance. Although hepatocellular carcinoma can arise in patients who have NAFLD without cirrhosis, the actual risk is unknown and probably very low. Until there are methods available to identify patients who are at increased risk, surveillance is not recommended for patients who have NAFLD without cirrhosis.

Abdominal ultrasonography every 6 months is the recommended method for surveillance, with or without measurement of serum levels of alpha-fetoprotein. The results are operator-dependent, with a sensitivity of 47 to 84% and a specificity higher than 90%.[36] The performance of ultrasound surveillance is problematic in obese patients. The role of computed tomography (CT) or magnetic resonance imaging (MRI) as a surveillance tool is unknown. Mutation analysis of circulating tumor DNA in the context of liquid biopsy has emerged as a potential new tool for early detection,[37] but its performance has yet to be established.

## DIAGNOSIS

In patients with cirrhosis, hepatocellular carcinoma can be diagnosed with the use of imaging techniques (Fig. 3) because of the vascular shift that occurs during malignant transformation of hepatocytes, in which benign lesions (e.g., regenerative and dysplastic nodules) are supplied by branches of the portal system, whereas malignant nodules are supplied by blood from the hepatic artery.[38] This shift translates into a distinctive pattern of hyperenhancement in the arterial phase and washout in venous or delayed phases on contrast-enhanced CT or MRI. This pattern has a sensitivity between 66% and 82% and a specificity higher than 90% for the diagnosis of hepatocellular carcinoma in patients with cirrhosis and nodules larger than 1 cm in diameter.[39] The Liver Imaging Reporting and Data System uses these and other features to classify hepatic nodules on the basis of the likelihood that they represent hepatocellular carcinoma.[40] Contrast-enhanced ultrasonography is also used to characterize liver nodules at expert centers, mostly in Europe[27] and Asia,[28] but its precise diagnostic role is still under investigation. For nodules with an inconclusive pattern on imaging or those in patients without cirrhosis, the diagnosis should rely on biopsy.

Establishing a histologic diagnosis in a patient with small nodules can be challenging, but a set of immunostaining markers — glypigan 3, heat shock protein 70, and glutamine synthetase — increase diagnostic accuracy.[41] Patients who have cirrhosis with nodules that are less than 1 cm in diameter should undergo ultrasound surveillance every 3 to 4 months and be considered for a return to conventional surveillance if the nodule is stable in size after 12 months.[27]

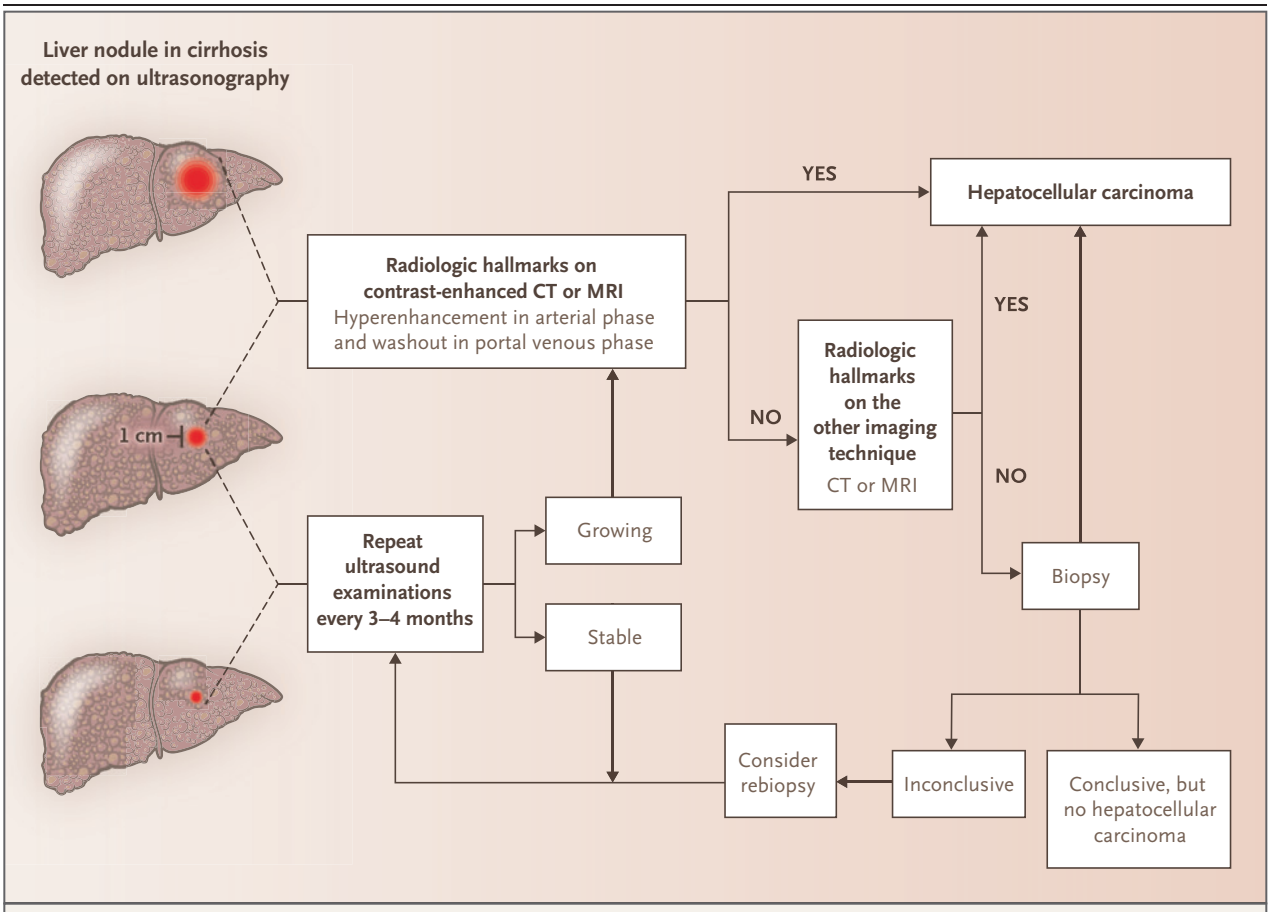


**Figure 3. Diagnostic Algorithm for a Liver Nodule in a Patient with Cirrhosis.**

The algorithm has been adapted from the guidelines of the European Association for the Study of the Liver.[27] Hepatocellular carcinoma in patients with cirrhosis can be diagnosed with the use of imaging techniques, depending on the size of the nodule and the pattern on radiologic imaging. If a nodule less than 1 cm in diameter remains stable in size after 12 months, a return to regular 6-month surveillance should be considered. The guidelines of the American Association for the Study of Liver Diseases recommend follow-up imaging as a possible alternative to biopsy for indeterminate nodules.[29]

## STAGING

Since most patients with hepatocellular carcinoma have concomitant liver disease, the benefits of treating the tumor must be balanced against the potential harms of medical interventions in patients with cirrhosis. This complexity in the management of hepatocellular carcinoma calls for a multidisciplinary approach, with expertise in hepatology, hepatobiliary surgery, pathology, oncology, radiology (both diagnostic and interventional), and specialized nursing. To adequately estimate survival, any staging system must quantify not only the tumor burden but also the extent of liver dysfunction and performance status. All these components are measured in the Barcelona Clinic Liver Cancer (BCLC) algorithm, which was introduced in 1999[42] and is the staging system most widely applied.[43] This algorithm is endorsed in clinical practice guidelines[27,29] and is the accepted benchmark for clinical trial design in hepatocellular carcinoma.[27] The algorithm classifies patients as being in one of five stages and provides treatment recommendations for each stage (Fig. 4). Other staging systems exist (e.g., the Hong Kong Liver Cancer staging system[44] and the Cancer of the Liver Italian Program[45]), but their implementation is restricted to certain geographic areas.

The tumor burden is quantified according to the number and size of nodules, along with the presence or absence of macrovascular tumor

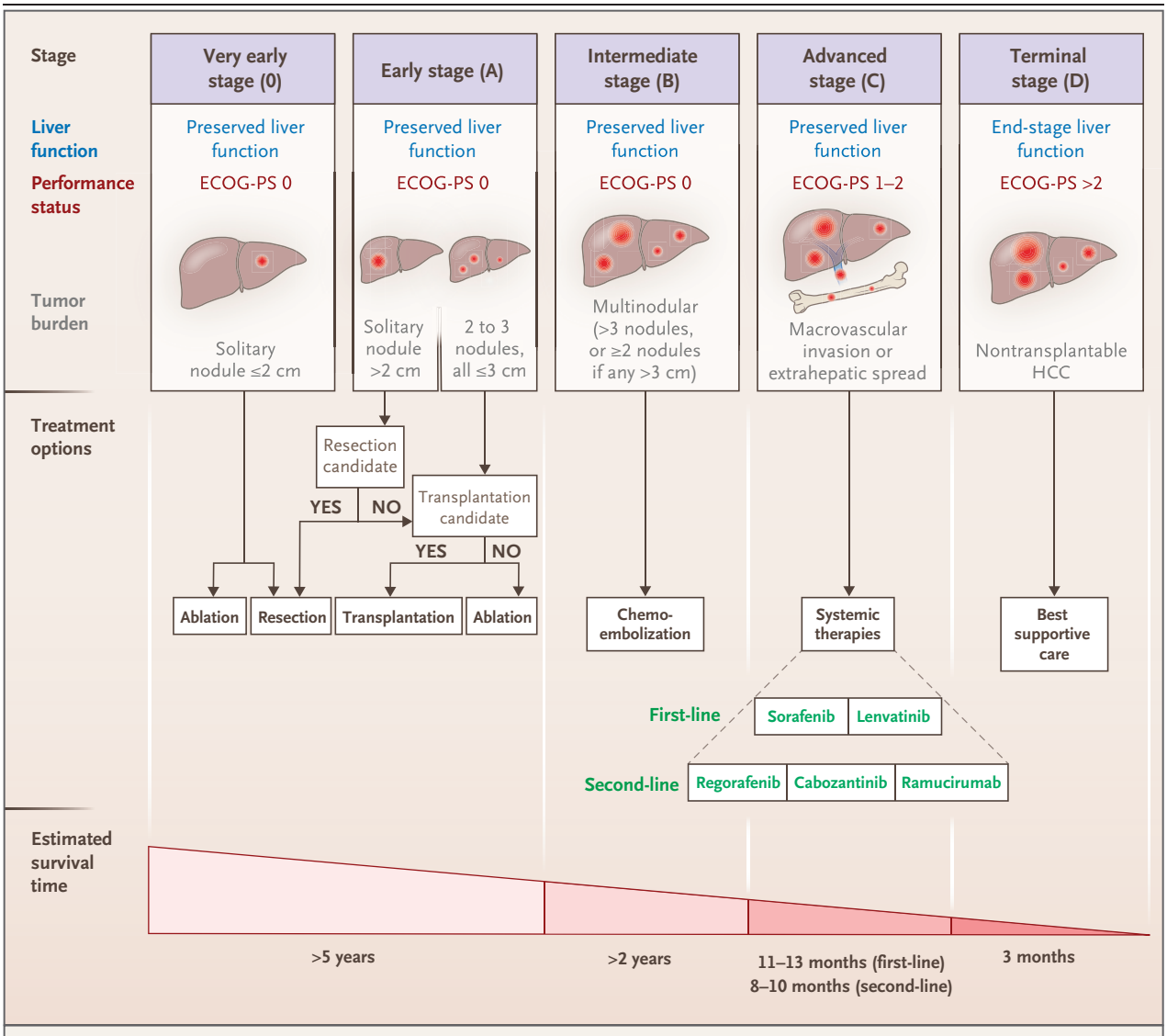


**Figure 4. Clinical Algorithm for the Management of Hepatocellular Carcinoma.**

The algorithm is based on the Barcelona Clinic Liver Cancer algorithm, which classifies patients as being in one of five stages, and European Association for the Study of the Liver guidelines.[27,43] Depicted is the estimated survival time in each stage once the recommended therapy has been administered or performed. The lenvatinib trial did not include patients with 50% or higher occupation of the liver with tumors or invasion of the bile duct or main portal vein. None of the second-line therapies were tested in patients who had tumors that had been treated with lenvatinib. Regorafenib was tested in patients for whom sorafenib was associated with an acceptable side-effects profile, and ramucirumab in those with serum AFP levels of 400 ng per milliliter or greater. Eastern Cooperative Oncology Group performance status (ECOG-PS) is a five-point scale on which higher numbers reflect greater disability. HCC denotes hepatocellular carcinoma.

invasion or extrahepatic spread, as assessed with cross-sectional imaging. For the assessment of liver dysfunction, the traditional Child–Turcotte–Pugh score (Table S2 in the Supplementary Appendix)[46] provides a subjective assessment and does not adequately capture the hepatic functional reserve. Alternatives include the Model for End-Stage Liver Disease[47] and the albumin–bilirubin grade.[48] All these assessment methods have limitations, but it is crucial to distinguish patients with well-preserved liver function from those with more advanced hepatopathy. In practical terms, patients with well-preserved liver function are those with compensated disease (i.e., no ascites)[49] and a Child–Turcotte–Pugh score of A on a scale of A to C, with C indicating

more liver dysfunction than A. These patients have the best outcomes across disease stages. A patient's general well-being and ability to perform certain activities of daily living without the help of others are measured with the Eastern Cooperative Oncology Group performance status, a five-point scale on which higher numbers reflect greater disability.[50]

## CLINICAL MANAGEMENT

### SURGICAL THERAPIES

The ideal candidates for resection are patients with a solitary tumor at an early stage (BCLC stage 0 or A), regardless of tumor size, in whom the performance status is good, liver function is well preserved, and there is no clinically significant portal hypertension.[51] For these patients, resection is associated with survival above 60% at 5 years, with low postoperative mortality (<3%); as many as 70% of these patients have tumor recurrence at 5 years.[52] No adjuvant therapies have been shown to reduce recurrence.[53] Despite improved prognostic stratification with the use of gene signatures in patients who have undergone resection,[12] this approach has not become part of routine clinical practice. A recent uncontrolled study involving HCV-infected patients with early-stage tumors who were receiving direct-acting antiviral agents showed an unexpectedly high percentage of patients with tumor recurrence after resection or ablation.[54] Subsequent studies,[55] including a meta-analysis, failed to confirm these results,[56] so additional data are needed to determine whether these drugs favor tumor recurrence.

Liver transplantation can be performed in patients with a limited tumor burden who are not candidates for resection. In addition to removing the tumor, transplantation has the advantage of curing the liver disease. The Milan criteria for liver transplantation (i.e., a single nodule ≤5 cm in diameter or up to three nodules, none larger than 3 cm in diameter) are the benchmark in patients with hepatocellular carcinoma[57] and have been adopted by the United Network for Organ Sharing (UNOS). Macrovascular tumor invasion or extrahepatic spread is a contraindication for transplantation because of the high risk of tumor recurrence. Transplantation in patients with tumors that meet the Milan criteria is associated with survival of 60 to 80% at 5 years and 50% at 10 years, with post-transplantation tumor recurrence lower than 15%. Transplantation in patients with tumors that do not meet the Milan criteria has worse outcomes.[58] Neoadjuvant treatments administered while patients are on the waiting list, generally ablation or transarterial therapies, are a cost-effective means of reducing the number of dropouts due to tumor progression when the median waiting time is longer than 6 months.[59] The use of these therapies to down-stage some tumors exceeding the Milan criteria (i.e., reducing the tumor burden to meet the criteria) is accepted by UNOS as a way of making formerly ineligible patients eligible for transplantation. The use of marginal grafts and living donation has increased the pool of organs available for transplantation. However, the gap between available donors and patients on the waiting list is still a major limitation of transplantation.

### TUMOR ABLATION

Ablation is recommended in patients with BCLC stage 0 or A tumors who are not candidates for surgery.[27,29] The main method is image-guided, percutaneous radiofrequency ablation, which achieves tumor necrosis by inducing a high intratumoral temperature. The extent of tumor necrosis is negatively correlated with tumor size and drops significantly in tumors larger than 3 cm in diameter. As compared with resection, ablation has fewer complications but provides worse local control for larger tumors. In some patients with solitary tumors that are less than 2 cm in diameter and in a favorable location within the liver parenchyma, radiofrequency ablation competes with resection as a recommended option for frontline treatment.[60] Other ablative options include microwave ablation, cryoablation, and ethanol injection. External-beam radiotherapy is safe, but randomized, controlled trials are needed to determine its efficacy and role in the management of hepatocellular carcinoma.

### TRANSARTERIAL THERAPIES

Patients with intermediate-stage tumors (BCLC stage B) should be considered for transarterial therapies. The main treatment method is transarterial chemoembolization (TACE), which entails intraarterial infusion of a cytotoxic agent, followed immediately by embolization of the vessels that feed the tumor. Adjacent nontumoral

liver tissue is generally protected from TACE because, unlike the tumor, its blood supply comes mainly from the portal vein. Two randomized, controlled trials and a meta-analysis that included positive and negative trials showed survival benefits with TACE as compared with the best supportive care.[61] A systematic review of TACE, including 101 studies and 12,372 patients, showed an objective response of 52.5%.[62] The mortality associated with TACE was below 1%, with most deaths due to liver failure,[62] a finding that underscores the importance of adequate patient selection for this therapy. TACE should not be considered in patients with decompensated cirrhosis. There is evidence that TACE performed with the use of drug-eluting beads has antitumoral activity similar to that of conventional TACE, with fewer side effects, whereas the use of bland embolization is more controversial. Median survival with TACE ranges from 26 to 40 months, depending on patient selection.[63,64] Combining TACE with the systemic drug sorafenib (an inhibitor of the serine–threonine kinases Raf-1 and B-Raf and the receptor tyrosine kinase activity of vascular endothelial growth factor receptors [VEGFRs] and platelet-derived growth factor receptor $\beta$ [PDGFR-$\beta$]) or brivanib (an inhibitor of VEGFR and fibroblast growth factor receptor) does not improve survival.[63,65]

Selective internal radiation therapy (SIRT) is another transarterial treatment approach frequently used in patients with BCLC stage B tumors. It is based on the intraarterial infusion of microspheres with the radioisotope yttrium-90. Unlike TACE, SIRT does not include a macroembolic step. The radiation emitted by yttrium-90 is responsible for its antitumoral activity. No randomized phase 3 trials have compared TACE and SIRT with respect to survival, but numerous cohort and retrospective studies indicate that SIRT is a safe procedure with an objective response similar to that seen with TACE.[66] The phase 3 clinical trials evaluating SIRT in patients with advanced disease (i.e., BCLC stage C) showed no improvement in survival with SIRT as compared with sorafenib and no improvement with SIRT and sorafenib combined as compared with sorafenib alone.[67-69]

### SYSTEMIC THERAPIES

Systemic therapies are recommended for patients who have advanced disease (BCLC stage C) or who have intermediate-stage disease (BCLC stage B) and progression with transarterial therapies. In the pivotal Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, survival increased from a median of 7.9 months with placebo to 10.7 months with sorafenib.[70] The safety and modest efficacy of this agent were validated in patients from the Asia–Pacific region.[71] Sorafenib was the first systemic drug approved by the Food and Drug Administration (FDA) for the treatment of hepatocellular carcinoma and is the standard of care for frontline therapy. Most agents and other treatment approaches subsequently tested in phase 3 trials failed to improve on or parallel the efficacy of sorafenib as frontline treatment; they also did not increase survival, as compared with placebo, for second-line treatment. These agents and treatments include erlotinib,[72] brivanib,[73,74] sunitinib,[75] linifanib,[76] everolimus,[77] pegylated arginine deiminase (ADI-PEG20),[78] SIRT,[67-69] hepatic arterial infusion chemotherapy,[79] doxorubicin,[80,81] and FOLFOX (fluorouracil, leucovorin [folinic acid], and oxaliplatin),[82] as well as tivantinib in patients with overexpression of MET[83] (Fig. 5). Insufficient antitumoral activity, toxicity in the context of cirrhosis, and inadequate patient selection have been proposed as reasons for these failures. Sorafenib remained the sole effective option for frontline therapy until lenvatinib, another inhibitor of multiple kinases, showed antitumoral activity in a noninferiority trial.[84] Median survival was 13.6 months with lenvatinib and 12.3 months with sorafenib. Grade 3 or 4 adverse events with lenvatinib included hypertension (in 23% of patients, vs. 14% receiving sorafenib), decreased weight (8% vs. 3%), and palmar–plantar erythrodysesthesia (3% vs. 11%). Lenvatinib received FDA approval for the treatment of hepatocellular carcinoma in 2018.

In recent years, substantial progress has been made in testing new, efficacious systemic therapies for hepatocellular carcinoma. Regorafenib, also an inhibitor of multiple kinases, increased survival, as compared with placebo, from 7.8 to 10.6 months among patients with tumor progression during treatment with sorafenib.[85] With a safety profile similar to that of sorafenib, regorafenib decreased the risk of death by 37%, as compared with placebo, and became the first drug approved by the FDA for second-line treatment. Other drugs that have shown efficacy as

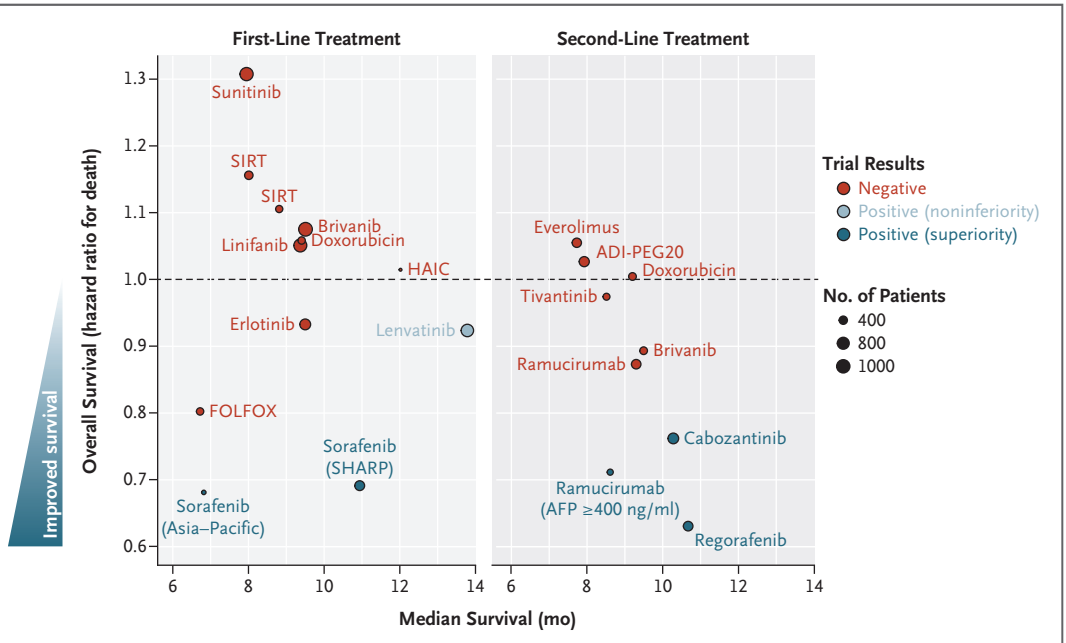


**Figure 5. Systemic Therapies Tested in Phase 3 Trials for the Management of Advanced Hepatocellular Carcinoma.**
ADI-PEG20 denotes pegylated arginine deiminase 20, HAIC hepatic arterial infusion chemotherapy, SHARP Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol, and SIRT selective internal radiation therapy.

second-line treatment in placebo-controlled trials are cabozantinib[86] and ramucirumab.[87] Cabozantinib, an inhibitor of receptor tyrosine kinases, including VEGFR, MET, and AXL, reduced the risk of death, as compared with placebo (hazard ratio, 0.76); grade 3 or 4 adverse events, mostly hypertension and palmar–plantar erythrodysesthesia, occurred in 68% of patients who received cabozantinib and in 36% of patients who received placebo. The ramucirumab trial enrolled patients with baseline alpha-fetoprotein levels of 400 ng per milliliter or greater. The trial was based on a post hoc analysis of a previous, negative trial that suggested efficacy in this subgroup.[88] Ramucirumab, an antibody against VEGF receptor 2, improved survival, as compared with placebo (hazard ratio for death, 0.71), with manageable toxic effects.

The clinical benefits of immune-based therapies for hepatocellular carcinoma are emerging. A small phase 2 trial with the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitor tremelimumab showed a partial response rate of 17.6%.[89] In patients who had disease progression or unacceptable adverse effects with sorafenib, treatment with the programmed cell death 1 (PD-1) immune checkpoint inhibitor nivolumab achieved a median survival of 15.6 months in a single-group phase 2 trial.[90,91] The overall response was 14.3% according to Response Evaluation Criteria in Solid Tumors (RECIST), and in 55% of the patients with a response, the duration of the response was more than 12 months.[92] These response data prompted FDA approval under the accelerated program. A phase 2 trial of pembrolizumab, another PD-1 inhibitor, showed a similar response (17%) but shorter survival (median, 12.9 months)[93]; in early 2019, the associated phase 3 trial of pembrolizumab for second-line treatment did not show longer overall survival or progression-free survival (the two primary end points) than placebo.[94] The tumor response to nivolumab correlates with survival,[91] underscoring the need for accurate biomarkers of the treatment response. Careful selection of patients who are most likely to have a response will spare other patients unnecessary toxic effects. The use of PD-1 ligand 1 staining to predict the response to nivolumab has had poor results,[90] and alternative predictors, such as tumor mutational burden, are under investigation. The combination of targeted therapies with im-

mune checkpoint inhibitors has been tested in phase 1 trials, including lenvatinib plus pembrolizumab[95] and atezolizumab plus bevacizumab,[96] with response rates of 46% and 32%, respectively. Ongoing phase 3 trials testing immune-based therapies will establish their role in the clinical management of hepatocellular carcinoma.

## FUTURE PERSPECTIVES

The increase in deaths due to hepatocellular carcinoma is a growing concern.[3] The hope is that universal HBV vaccination, the increasing cure rates of HCV infection, and improvements in surveillance will reduce this burden. Hepatocellular carcinoma is a complex disease, frequently associated with cirrhosis; a multidisciplinary approach in specialized clinics is required to maximally influence the course of the disease. The clinical management of hepatocellular carcinoma has improved in the past 10 years, particularly for patients at advanced stages. Other areas of management remain without effective interventions, such as chemoprevention in patients with cirrhosis and adjuvant therapies after surgical resection or ablation. As the number of systemic agents found to be effective in phase 3 trials continues to grow, the challenge is to determine the order of sequential systemic therapy that maximizes the clinical benefit with minimal toxic effects and cost. The prospect of combination therapies and the use of systemic drugs at earlier stages will shape research initiatives for hepatocellular carcinoma in the near future.

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Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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