Evidence-based management of patients with hepatocellular carcinoma (HCC) is key to their optimal care. For individuals at risk for HCC, surveillance usually involves ultrasonography (there is controversy over use of biomarkers). A diagnosis of HCC is made based on findings from biopsy or imaging analyses. Molecular markers are not used in diagnosis or determination of prognosis and treatment for patients. The Barcelona Clinic Liver Cancer algorithm is the most widely used staging system. Patients with single liver tumors or as many as 3 nodules ≤3 cm are classified as having very early or early-stage cancer and benefit from resection, transplantation, or ablation. Those with a greater tumor burden, confined to the liver, and who are free of symptoms are considered to have intermediate-stage cancer and can benefit from chemoembolization if they still have preserved liver function. Those with symptoms of HCC and/or vascular invasion and/or extrahepatic cancer are considered to have advanced-stage cancer and could benefit from treatment with the kinase inhibitor sorafenib. Patients with end-stage HCC have advanced liver disease that is not suitable for transplantation and/or have intense symptoms. Studies now aim to identify molecular markers and imaging techniques that can detect patients with HCC at earlier stages and better predict their survival time and response to treatment.

**Keywords:** Liver Cancer; BCLC; Early Detection; Therapy.

Approximately 700,000 people die of hepatocellular carcinoma (HCC) each year worldwide, making it the third leading cause of cancer death. In the United States and Canada, HCC is the only cancer for which mortality is increasing due to the high prevalence of chronic hepatitis C, immigration from areas where hepatitis B and hepatitis C are common, and the epidemic of nonalcoholic fatty liver disease. The incidence of intrahepatic cholangiocarcinoma might have also increased, but less than 10% of patients with primary liver cancer have this cancer type. In this review, we do not discuss cholangiocarcinoma or the fibrolamellar variant of HCC, which has epidemiological features that differ from those of other HCCs.

Patients with HCC usually present with symptoms of cancer and liver failure unless the cancer is detected at an early stage. Very advanced HCC is untreatable, and most patients die within 3 to 6 months. However, HCC has a prolonged subclinical growth period during which interventions can be performed and patients can be cured. We review the evidence to support current methods of surveillance, diagnosis, staging, and treatment of HCC as well as new treatment approaches.

**Surveillance of HCC**

**Identification of Patients at Risk**

The most significant risk factor for HCC is cirrhosis. Not all patients with cirrhosis are at equal risk for HCC, and HCC is not always found in patients with cirrhosis. There are no reliable data on the incidence of HCC in patients without cirrhosis. In addition to cirrhosis, other factors associated with increased risk include male sex, older age, persistent increase in alanine aminotransferase level, increased α-fetoprotein (AFP) level, and progressive impairment of liver function. However, knowing that a patient has a risk factor does not aid in the decision of whether to offer surveillance, because risk varies within the population identified by any one risk factor. Increased risk is not sufficient to make surveillance worthwhile; the decision to offer surveillance must also consider the patient’s likelihood of receiving treatment if he or she is found to have HCC. If the severity of liver disease and/or comorbidities indicates that effective treatment is impossible, there is no benefit of surveillance.

Guidelines from the American Association for the Study of Liver Diseases (AASLD) were developed on the basis of cost-effectiveness analyses and the risk of HCC in defined populations. More sophisticated models have since produced a number of risk scoring systems (Table 1). However, these are not yet ready for general use. Most have not been validated, and many were developed in defined populations.
populations. Only one report has translated degree of risk into a decision of whether or not to provide surveillance.\textsuperscript{19} Other studies presume that patients at highest risk require surveillance; however, among those with lower levels of risk, there is no reliable cutoff value below which surveillance is unnecessary. Finally, risk scoring systems were all developed in untreated populations and may not perform equally well in treated patients.

Liver stiffness has also been used to predict risk of HCC, either individually or in combination with a risk score,\textsuperscript{22–24} but a threshold for institution of surveillance has not been adequately defined. The AASLD criteria for surveillance are very broad; in the absence of a defined risk threshold, it is probably wise to err on the side of being more inclusive and apply the AASLD incidence cutoff of 1.5% – 2% for patients with cirrhosis and 0.2% for patients with chronic hepatitis B.

### Evidence to Support Surveillance and Its Methodology

Surveillance of HCC is controversial.\textsuperscript{25} The evidence to support surveillance primarily comprises demonstration of stage migration and more frequent application of potential curative treatment in screened populations. There have been 2 randomized trials of HCC surveillance, and both were performed in China.\textsuperscript{26,27} One used AFP level at screening,\textsuperscript{26} and the other used AFP level plus findings on ultrasonography.\textsuperscript{27} The first study failed to show a benefit of surveillance. The second study found a 37% reduction in mortality with surveillance, but this study has been heavily criticized. Nonetheless, in balancing potential benefit versus potential harm, the equation clearly tilts toward surveillance. The most impressive data from a prospective study that supported surveillance came from an analysis of a Taiwanese population in which subjects were selected for surveillance based on a risk score.\textsuperscript{28} Mortality in the group that received surveillance was reduced compared with the control group and the general population. Virtually all cost-effectiveness analyses of surveillance find it to be effective and cost-effective according to accepted definitions.\textsuperscript{29–36}

Patients with HCC identified by surveillance present with smaller tumors and are more likely to undergo a curative procedure.\textsuperscript{37–39} These cohort studies are subject to lead time and length bias, which cannot be completely avoided (Figure 1). A recent meta-analysis\textsuperscript{40} concluded that despite poor-quality evidence, HCC surveillance increased the life expectancy of patients with cirrhosis.\textsuperscript{41} However, a systematic review concluded that there was insufficient evidence to recommend surveillance.\textsuperscript{42} Because clinicians who care for patients with liver disease all too often see unscreened patients presenting with advanced HCC, an a priori argument can be made that patients at risk should undergo surveillance, at least until there is evidence that surveillance is inefficient.

Ultrasonography is the recommended method of surveillance for HCC.\textsuperscript{35,50,43} There is controversy over use of assays that measure levels of AFP, des-\gamma-carboxy prothrombin,
or the L3 fraction of AFP to detect HCC because there is little evidence that they contribute to early detection or improve patient outcomes. Increased concentrations of these markers are associated with features of poor prognosis, including large tumors, invasion of the portal vein, and poor differentiation of HCC cells. Surveillance aims to find small lesions in patients with a good prognosis profile if treated, so biomarkers of poor outcomes are unlikely to be useful for early detection of HCC. Quantiﬁcation of AFP identiﬁes patients with HCC with only approximately 60% sensitivity; AFP levels are increased in some patients with cirrhosis, chronic hepatitis, or cholangiocarcinoma, so rates of false-positive results are high. The data available for tests to measure des-γ-carboxy prothrombin and the L3 fraction of AFP are not sufﬁcient to recommend them. Serial assessment of levels of AFP, des-γ-carboxy prothrombin, and the L3 fraction of AFP has been proposed, but little is known about the sensitivity and speciﬁcity of this strategy for detection of HCC.

Figure 1. Changes in diagnosis and treatment of HCC over time. Years ago, techniques such as ultrasonography, computed tomography, and magnetic resonance imaging were not available. Therefore, HCC was almost always diagnosed when the cancer produced symptoms. Progression registration, either symptomatic or at mere palpation or imaging, would closely precede death. Years later, it became feasible to diagnose HCC at earlier stages, before symptoms developed. Registration of progression was no longer so close to death, which probably occurred at the same time point irrespective of treatment. This illustrates the lead-time bias induced by earlier detection in the absence of effective treatment or suboptimal treatment intervention. Patients are now diagnosed with early-stage disease due to surveillance programs. The best therapy can now be selected for each patient, increasing survival times. Interestingly, recurrence or progression after treatment now occurs far in advance of death, so there may no longer be a correlation between progression and death. Progression-free survival is therefore not an informative end point for clinical trials of patients with HCC; the main end point should be survival time.

or the L3 fraction of AFP to detect HCC because there is little evidence that they contribute to early detection or improve patient outcomes. Increased concentrations of these markers are associated with features of poor prognosis, including large tumors, invasion of the portal vein, and poor differentiation of HCC cells. Surveillance aims to find small lesions in patients with a good prognosis profile if treated, so biomarkers of poor outcomes are unlikely to be useful for early detection of HCC. Quantiﬁcation of AFP identiﬁes patients with HCC with only approximately 60% sensitivity; AFP levels are increased in some patients with cirrhosis, chronic hepatitis, or cholangiocarcinoma, so rates of false-positive results are high. The data available for tests to measure des-γ-carboxy prothrombin and the L3 fraction of AFP are not sufﬁcient to recommend them. Serial assessment of levels of AFP, des-γ-carboxy prothrombin, and the L3 fraction of AFP has been proposed, but little is known about the sensitivity and speciﬁcity of this strategy for detection of HCC.

Ultrasonography detects small HCCs with a high level of sensitivity, although ﬁndings vary among operators and patients. With the best operators, ultrasonography identiﬁes patients with HCC with approximately 80% sensitivity; for most operators, the level is closer to 65%. The dome of the liver can be hard to view, and obesity or fatty liver make visualization difﬁcult. Finally, differentiating a small HCC from a regenerative cirrhotic nodule is also difﬁcult. Surveillance by computed tomography or magnetic resonance imaging is not recommended because of radiation risks, high cost, and high rates of false-positive results.

Tumor doubling time and ﬁndings from cohort studies indicate that the best screening interval is 6 months. Examining patients every 3 months did not increase survival time but led to more diagnostic investigations. A study in Asia compared 4-month versus 12-month surveillance intervals and found no difference in patient survival after 4 years. However, there were too few deaths to be informative. A large study showed that a higher proportion of patients survived when they underwent surveillance every 6 months compared with every year.

Diagnosis

Patients can be diagnosed with HCC based on imaging or biopsy analyses. The speciﬁc imaging patterns observed by magnetic resonance imaging or computed tomography analyses in nodules >10 mm in cirrhotic livers or livers of patients at high risk for HCC are intense uptake of contrast during the arterial phase followed by contrast washout in the venous or delayed phases. HCCs contain mostly arterial blood and are therefore brighter during the arterial phase than the surrounding liver, which contains arterial and venous blood. In the venous phase, the HCC is less bright because it contains contrast-free arterial blood, whereas the liver contains venous blood with contrast. This dynamic pattern identiﬁes HCCs with limited levels of sensitivity but with close to 100% speciﬁcity. In the absence of this typical appearance, a biopsy is required to detect HCC. The speciﬁcity values are not quite as high for contrast-enhanced ultrasonography.
In histological analyses, small nodules detected by surveillance may be very early-stage HCCs or low- or high-grade dysplastic nodules. Very early HCC is morphologically and radiologically different than progressed HCC. It is usually hypovascular because the arterial blood supply has not fully developed. It is as well differentiated as high-grade dysplasia. Fat may be present, and microvascular invasion is rare. Malignancy is recognized by the presence of stromal invasion (hepatocytes in the portal tract), which a needle biopsy may miss. More advanced or progressed HCC is less often well differentiated and can have a well-defined capsule and microvascular invasion. Immunohistochemical analyses of heat shock protein 70, glypican 3, glutamine synthetase, and clathrin heavy chain can be used to confirm a diagnosis of HCC, but they do not replace the need for an expert pathologist. Assays to measure expression of telomerase, glypican 3, LYVE1, or survivin have been proposed but not validated. Radiological analyses detect HCC with high levels of specificity, so biopsy analysis is no longer necessary for many patients. Some have advocated that biopsies should be performed on all HCCs for research purposes. This requires informed consent. Lesions identified by surveillance must be characterized. In any cancer screening program, there is the possibility of overdiagnosis. To minimize this risk, a recall algorithm has been developed and validated. Lesions <10 mm are unlikely to be HCC and thus require only a short-interval follow-up period, such as every 3 months for at least 2 years. Lesions ≥10 mm are more likely to be HCC. If computed tomography or magnetic resonance imaging evaluations show typical features of HCC, no further investigation is required. If the features are not typical, alternate imaging procedures can be performed or a biopsy specimen can be collected and analyzed. A negative finding from biopsy analysis does not exclude HCC because it is difficult to distinguish between early-stage HCC and dysplastic nodules and also because of sampling errors. If suspicion is sufficiently strong, a second biopsy specimen can be collected from the lesion and analyzed. If not, the lesion should be watched for any change that might prompt further analysis.

Staging

The Barcelona Clinic Liver Cancer (BCLC) system has been widely validated and is the most commonly used staging system for HCC (Figure 2). It determines cancer stage and patient prognosis based on tumor burden, severity of liver disease, and the patient's performance status. Very early and early-stage HCC (BCLC 0 or BCLC A) include patients with a solitary lesion or up to 3 nodules ≤3 cm (without macrovascular invasion or extrahepatic spread) with preserved liver function. Patients can benefit from potentially curative treatments (resection, transplantation, or ablation). Patients with intermediate-stage HCC (BCLC B) do not have symptoms, but they have large, multifocal tumors without vascular invasion or spread beyond the liver. If liver function is preserved, they may be candidates for transcatheter chemoembolization (TACE). The current definition of intermediate-stage HCC encompasses a wide range of patients that can be stratified. However, patients with large solitary HCCs (≥5 cm) without vascular invasion are assigned to the BCLC A group; if technically feasible, these patients benefit from resection. Also, it is important to remember that Child–Pugh class A or B can include patients with ascites, in whom bacterial peritonitis, renal failure, or recurrent encephalopathy are predictive of poor outcomes. These patients should be considered for transplant unless tumor burden exceeds listing criteria. If so, the patient's disease should be classified as end stage.

Patients with advanced-stage HCC (BCLC C) have tumors that have spread beyond the liver and/or vascular invasion and/or mild cancer-related symptoms (Eastern Cooperative Oncology Group [ECOG] grades 1–2). The tyrosine kinase inhibitor sorafenib is the only treatment found to prolong survival. Patients with end-stage disease (BCLC D) have poor liver function (Child–Pugh class C, high Model for End-Stage Liver Disease [MELD] scores) and are not candidates for transplantation and/or have marked cancer-related symptoms (Performance Status >2). They have a poor prognosis and require supportive care.

Measurements of AFP might be useful for prognosis of patients in research trials, but in practice, an increased level of AFP will not affect treatment strategy; prognostic factors are not used to determine therapy. It was recently proposed that liver function be evaluated using individual parameters of the Child–Pugh score (albumin and bilirubin level). A more complex model, based on findings from a retrospective analysis of a large cohort of treated patients (mostly with hepatitis B), combined outcome analysis with treatment preferences. It has not been validated, and the outcome stratification is suboptimal.

Molecular Markers of Risk, Diagnosis, and Determination of Prognosis and Treatment

Recent insights into mechanisms of HCC pathogenesis as well as studies of large sets of tumors and patients have identified factors that might be used in determining patients’ risk of HCC, their prognosis, or the best treatment. However, translation of findings from studies of cells and experimental models requires clinical trials. Most analyses have been based on retrospective studies of tumor and patient samples from tissue banks. Clinical information has been limited and does not incorporate variables that are currently used to estimate risk (such as portal hypertension, which predicts tumor development) or predict survival. Gene expression signatures from surrounding liver can indicate different stages of cirrhosis, along with activation of stellate cells, rather than risk of tumor development.

In most studies, tumor samples were collected during resection and then compared with patient outcomes; these samples do not represent the tumors of patients with advanced-stage disease, who do not undergo surgery. In addition, there is much heterogeneity within each tumor
nodule and among separate nodules. This poses a major challenge to the use of molecular analyses of biopsy specimens to determine prognosis or select treatment (see Pinyol et al100 and Borel et al101 for reviews on this subject).

Treatment
The end point of treatment is to increase survival. Treatments should not be offered because they are technically possible. Treatment indications have been redefined, and if patients are not candidates for first-line therapy as per stage, they can be given the treatment for a more advanced-stage tumor (treatment stage migration; see Figure 3).82

**BCLC Stage 0**
Surgery is no longer the only first-line treatment. Resection, transplantation, and ablation provide excellent results for single lesions ≤2 cm (T1 stage) in patients with preserved liver function. Rates of 5-year survival range from 60% to 80%.105,106 Although there has been no robust trial to compare the efficacy of surgery versus ablation,107 case-control and modeling studies have shown ablation to be noninferior and more cost-effective for patients with very early-stage HCCs.108,109 There are no data to guide decision making for small tumors when patients may be candidates for all options. Some have reserved liver transplantation for patients with recurrence of cancer after treatment.110 Others

*Note that Child-Pugh classification is not sensitive to accurately identify those patients with advanced liver failure that would deserve liver transplant consideration.

**Patients with end stage cirrhosis due to heavily impaired liver function (Child-Pugh C or earlier stages with predictors of poor prognosis, high MELD score) should be considered for liver transplantation. In them, HCC may become a contraindication if exceeding the enrollment criteria.

Figure 2. Staging and treatment according to the BCLC system. The first step in evaluation of patients combines prognosis (upper section) with selection of treatment (lower section). Prognoses are made based on clinical and tumor parameters. As in all recommendations, the treatment should be selected based on a detailed evaluation of characteristics such as the patient’s age and comorbidities. As mentioned in the text, the Child–Pugh classification is not sensitive enough to accurately identify patients with advanced liver failure who would deserve consideration for liver transplantation. Some patients corresponding to Child–Pugh class B, and even Child–Pugh class A, could have poor outcomes because of events such as spontaneous bacterial peritonitis, recurrent variceal bleeding, refractory ascites, hepatorenal syndrome, recurrent encephalopathy, or severe malnutrition, which are not registered in the Child–Pugh classification. Patients with end-stage cirrhosis due to heavily impaired liver function (Child–Pugh class C or earlier stages with predictors of poor outcome, or high Model for End-Stage Liver Disease [MELD] scores) should be considered for liver transplantation. In these patients, HCC may become a contraindication if it exceeds the enrollment criteria. Modified with permission from Forner et al81 and Reig et al.82
have proposed resection as a first approach, reserving liver transplantation for patients with microvascular invasion or satellites detected by pathological analysis. Resection and transplantation produce the best outcomes for well-selected candidates with HCC of BCLC stage A; 60% to 80% of patients survive for 5 years. These approaches compete as the first treatment option for patients with early tumors, well-preserved liver function, and no clinically significant portal hypertension. Patients should be assessed for resection and transplantation to identify those who would have better outcomes than they would with other treatments. Treatment should be chosen based on predicted immediate-term and long-term survival. Liver function is not accurately evaluated by Child–Pugh score. Clinically significant portal hypertension predicts poor outcomes for patients with or without HCC and has negative effects on mortality and morbidity. Transplantation should be considered for patients with clinically significant portal hypertension; 70% of patients survive for 5 years with adherence to the Milan criteria. Patients who are not suitable for surgery because of comorbidities should be considered for treatment with ablation.

The Milan criteria (single HCC ≤5 cm or ≤3 nodules each ≤3 cm and no macrovascular invasion on imaging) are used to select patients for liver transplantation. A meta-analysis found that patients who met the Milan criteria had longer survival times than patients with larger tumor burdens. Nevertheless, the Milan criteria are often considered to be restrictive, so expanded criteria have been proposed. The University of California San Francisco criteria have been partially validated but have much overlap with the Milan criteria and at best would increase the proportion of patients available for liver transplantation by approximately 5%.

Outcomes after liver transplantation can be predicted as a continuous function based on different combinations of tumor size and number (see http://www.hcc-olt-metro-ticket.org/calculator). Patients with tumors within the up-to-7 rule without microvascular invasion at explant achieve competitive outcomes with respect to conventional criteria. This pathology-based proposal requires prospective validation using radiological findings collected before liver transplantation. The AFP level has been reported to improve the predictive ability of the Milan criteria or the combination of AFP level (especially >400 ng/mL) and total tumor volume rather than tumor size and number, with a total tumor volume cutoff of 115 cm³. In general, patients with HCC on the waiting list for transplantation with a baseline serum AFP level of >200 ng/mL have significantly worse outcomes, although the most significant adverse determinant is a steady increase of AFP level >15 ng/mL per month. Cutoff AFP levels of 300 ng/mL, 400 ng/mL, and 1000 ng/mL have been proposed for removal of patients from the waiting list for liver transplantation.

The major limitation for successful transplantation is organ shortage. Resection, ablation, chemoembolization, and radioembolization are commonly used to avoid unacceptable progression (bridge therapy). However, there is little evidence to support this approach. Liver donations from living, related donors and deceased donors have not had significant effects on transplant rates except in some jurisdictions. The heterogeneity of tumor presentation and the variability of response to treatment make accurate predictions of progression, effective transplantation, and survival difficult for patients with HCC. No equitable priority approach for all patients on the waiting list for liver transplantation is available.

Down-staging is defined as the reduction of the HCC burden to meet acceptable criteria, based on expected survival after liver transplantation that is equal to that of patients who meet transplant criteria without down-staging. Most programs use TACE to down-stage to Milan Criteria (MC), and this status should be maintained for at least 3 to 6 months. The lack of a validated approach for staging, assessment of down-staging and
delisting, and robust intention-to-treat analysis has prevented the endorsement of this strategy.130,131

Radiofrequency (RFA) is now the first-line ablation technique, and microwave ablation is becoming a competitor. Ethanol injection provides less local control but still has a role in achieving a complete response when there is minimal residual viable tissue. All techniques achieve the same effectiveness and survival in solitary HCC ≤2 cm, with portal hypertension as the main determinant of outcome. Survival of patients with HCC ≤3 cm treated by RFA is similar to that offered by resection.152 Either approach could therefore be considered first-line therapy, and consideration should be given to age, comorbidities, and tumor location. In patients with HCCs >3 cm or multifocal HCCs, the rate of failure of ablation increases,133,134 in which case resection (for a single HCC) may offer a better outcome. Combined treatment with chemoembolization and ablation has been proposed,135 but robust conclusions cannot be made from the studies performed. The rate of recurrence after ablation of tumors ≤3 cm is the same as after surgical resection, although anatomic resection may achieve better local control.

Validated predictors of recurrence are tumor size, multifocality, macroscopic and microscopic vascular invasion, and poor differentiation.943,136 Early recurrence (<2 years) is likely due to intrahepatic metastasis, whereas later recurrence is supposedly due to metachronous HCC.136 This division has not been established; late recurrences could also arise due to a lower capacity of the tumor cells for dissemination or proliferation. There is no effective approach to reduce the rate of recurrence,9,43,137 and there is no preferred immunosuppressive regimen after transplant.126,138

**BCLC Stage B**

Patients with HCC of BCLC stage B should be considered for TACE. Conventional TACE (c-TACE) involves intra-arterial infusion of chemotherapy (usually doxorubicin or cisplatin), frequently mixed with Lipiodol (ethyolized oil) to increase exposure of the tumor to the drug, followed by embolization of the feeding vessel(s) with agents such as gelatin sponge.139 This causes cytotoxicity and ischemia. Randomized controlled trials have shown that TACE increases survival time.108,141 The median survival time was 28.7 months for patients receiving c-TACE versus 17.9 months for control patients in a BCLC trial140 and 18 months versus 9.2 months in a trial in Hong Kong14 in which patients with portal vein invasion were excluded. A cumulative meta-analysis showed that c-TACE increased the proportions of patients who survived 2 years and established it as the treatment for intermediate-stage HCC.9,43,143,144

Not all patients with intermediate-stage HCC can be considered for TACE. Some absolute and relative contraindications exist,83 including tumor burden (size >10 cm) and impairment of liver function. The best candidates for TACE are asymptomatic patients with a solitary or limited multifocal HCC without vascular invasion or extrahepatic spread and with well-preserved liver function (Child–Pugh class A or B-7 points without ascites).9,43,144 In these patients, selective TACE is well tolerated (serious adverse events such as liver failure or abscess affect <5% of patients) and achieves a high rate of objective responses. Favorable outcomes are achieved with c-TACE or TACE with drug-eluting beads (DEB-TACE), which slowly release chemotherapy after embolization to increase tumor exposure to chemotherapy and reduce systemic drug exposure. Survival after DEB-TACE is not different from that after c-TACE, but the treatment is more reproducible and better tolerated. A randomized phase 2 trial showed a significant reduction in doxorubicin-related adverse events; a later trial in Italy confirmed the better tolerance of patients to DEB-TACE.147

Cohort studies with an adequate selection of candidates140,149 have reported median survival beyond 40 months after DEB-TACE. The same survival figures are reported with c-TACE,150 and rates of complications are the same with both techniques. Less stringent selection criteria affect outcomes.151,152 If TACE is properly applied, median survival times should not less than 30 months.

There are some unanswered questions about TACE. The combination of TACE and RFA might provide a therapeutic benefit for patients’ tumor burdens that are unlikely to have a complete response to either therapy alone.153 Trials that combine TACE with RFA have either recruited patients with early-stage HCC and/or compared TACE and RFA with RFA alone instead of TACE and RFA compared with TACE alone.135

It is important to remember that the efficacy of TACE depends on complete obstruction of the tumor vasculature.199 Treatment that aims to merely achieve selective delivery of chemotherapy using any type of carrier and not complete vascular obstruction is likely to be less effective.142 Similarly, because angiogenic factors peak after TACE,154 treating first one lobe and the other 1 month later could potentially stimulate tumor proliferation in the initially untreated lobe. No study has properly evaluated whether on-demand TACE, according to tumor response, increases survival compared with TACE at regular intervals. Adjuvant treatment with sorafenib155 or brivanib156 has not improved outcomes.

One important decision is when to stop TACE. In oncology, disease progression is taken as treatment failure. However, with locoregional therapies, some forms of progressing disease (regrowth of an initially responsive tumor or appearance of a new hepatic nodule) can be successfully re-treated.165 This justifies the concept of untreatable progression (progression in which re-treatment is contraindicated).152 TACE should not be repeated when substantial necrosis is not achieved after 2 initial rounds of TACE, when follow-up treatment fails to induce marked necrosis at sites that have progressed after initial response, when major progression (substantial liver involvement, vascular invasion, or extrahepatic spread) occurs after an initial response, and when re-treatment is unsafe because of deterioration of liver function. Poor tolerance to TACE, based on clinical or biochemical findings or a scoring system (such as the Assessment for Retreatment with TACE score),151 is a contraindication for additional TACE. However, it may be
that patients identified as poor candidates for additional TACE were already poor candidates for TACE in the first place according to guidelines.9,43,144

In some settings, resection will be offered irrespective of portal hypertension, degree of impairment of liver function, or multifocal disease115,157,158 because surgery has the potential to cure the patient. No studies have directly compared outcomes of patients after surgery (or TACE) beyond current recommendations with nonstandard treatments. Some patients may benefit from more aggressive treatment, but there are no data on whether those who do not benefit have been at a disadvantage because they have not been treated per guidelines112; findings from studies of international registries indicate this to be the case.158

BCLC Stage C

Conventional chemotherapy, administered intravenously or intra-arterially, is ineffective for patients with HCC.9,43,144 In some centers, the intra-arterial injection of chemotherapy is performed using an emulsion in ethiodized oil, aiming to increase tumor exposure and reduce systemic toxicity. However, the emulsion is unstable and the survival benefits have not been established.

Sorafenib is an inhibitor of many kinases that reduces tumor cell proliferation and angiogenesis and increases tumor apoptosis.159 It also induces major changes in stromal cells. In a phase 3 trial performed in the West,88,160 sorafenib reduced patients’ risk of death by 30% (median survival time of 10.7 months with sorafenib vs 7.9 months without). In a trial performed in the East,161 patients had shorter survival times because they entered the study with more advanced-stage HCC; median survival times were 6.5 months with sorafenib versus 4.2 months without. The magnitude of improvement was the same in each study, indicating that the drug is active in different populations.162

There are no biomarkers for response.163 Sorafenib delays tumor progression, because patients have marginal reductions in tumor burden.88,161 The most frequent adverse events are hand/food/skin reactions, asthenia, diarrhea, and arterial hypertension,88,161 the incidence of which is higher in Asian patients. Up to 30% of the patients have to discontinue treatment because of adverse events,164 but adverse events correlate with a better outcome.165 Careful management of patients and appropriate dose adjustments are therefore needed.

Sorafenib is now the standard systemic therapy for HCC. It is the first treatment option for patients with HCC of BCLC stage C9,43,144,165 and for patients with HCC of BCLC stages A or B who are not candidates for curative or locoregional treatments due to treatment stage migration and/or untreatable progression because of tumor burden.82,83,166

Several agents have been evaluated in phase 3 trials as first- and second-line treatments for HCC.167–173 None have exceeded the benefits of sorafenib, or placebo in second-line treatment, despite suggestive findings from early-stage studies.174–184 This indicates that inappropriate markers of efficacy were used in the earlier trials. The criteria to assess preclinical and early clinical studies should be improved. Drugs could have activities that do not produce conventional responses such as tumor shrinkage or lack of growth. Time to progression may also be equivocal because progression at imaging may not represent treatment failure. This was the reason that treatment was continued beyond progression in the sorafenib trials160,185 with refinement of the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.12 Table 2 shows that differences in time to progression have not always translated in improved survival. This may reflect the existence of a heterogeneous progression pattern (Figure 4) and/or a potential drug toxicity that counterbalances the activity of the drug. Assessment of contrast uptake by computed tomography and magnetic resonance imaging, as proposed by modified RECIST criteria,186 has not been validated yet as a surrogate of sorafenib efficacy. Interobserver or intraobserver differences may become an issue in large multifocal disease. Similarly, definition of progression, based on modified RECIST criteria, requires recognition of washout and not just the hypervascularity of nodules >10 mm. Thus, in the absence of validation studies that establish the most accurate criteria, reported data on time to progression must be filtered according to the criteria used. Finally, there has been much effort in selecting patients for trials based on molecular features of tumors. The concept is sound and has been used in treatment of other neoplasms with factors shown to promote tumor development (breast, colorectal, lung) but has not yet been applied to patients with HCC. The heterogeneity of HCC99,187 poses a major challenge for this approach.

BCLC Stage D

Patients with HCC of BCLC stage D have no treatment options, either because of their extensive tumor or advanced liver disease.90 Their prognosis is poor, and they should receive the best supportive care.90

Treatments in Development

Radioembolization

Radioembolization is the intra-arterial injection of microspheres loaded with yttrium-90, a pure β-emitter with a short half-life (2.67 days) and a limited capacity to penetrate tissues (mean depth of penetration of 2.5 mm; maximum of 11 mm). Two types of yttrium-90 microspheres are commercially available: glass (TheraSphere; BTG, London, United Kingdom) and resin microspheres (SIR-Spheres; Sirtex SIR-Spheres Pty Ltd, Sydney, Australia).188 The efficacy of radioembolization has been assessed in prospective studies with promising results in tumor response189 and survival.190–192 Because yttrium-90 is attached to small beads, the technique does not cause substantial ischemia, minimizing the incidence of the post-embolization syndrome.193 Although radioembolization is usually well tolerated, there may be severe effects due to irradiation of other organs.194 Radioembolization has been linked to a form of sinusoidal obstruction syndrome known as radioembolization-induced liver disease, which develops
Table 2. Results of Phase 3 Trials of First and Second-Line Treatments Assessing the Efficacy of Targeted Therapies in HCC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Author</th>
<th>Year</th>
<th>Drug</th>
<th>n</th>
<th>Child–Pugh class A/B/C (%)</th>
<th>PS 0/1/2 (%)</th>
<th>BCLC B/C (%)</th>
<th>Drug scheme</th>
<th>Criteria</th>
<th>Scheme</th>
<th>Treatment discontinuation criteria</th>
<th>Time to progression (mo)</th>
<th>P value</th>
<th>OS (mo)</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Sorafenib 800 mg orally twice daily</td>
<td>Modified WHO criteria</td>
<td>8 wk</td>
<td>Stop at disease progression</td>
<td>5.5</td>
<td>9.2</td>
<td></td>
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<td>72/28/0</td>
<td>50/50/0</td>
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<td></td>
<td>3</td>
<td>Llovet et al</td>
<td>2008</td>
<td>Sorafenib vs placebo</td>
<td>299/303</td>
<td>95/5/0</td>
<td>54/38/8</td>
<td>18/82</td>
<td>RECIST + amendment</td>
<td></td>
<td>6 wk</td>
<td>Treatment could continue beyond radiographic progression</td>
<td>5.5 vs 2.8</td>
<td>&lt;.001</td>
<td>10.7 vs 7.9</td>
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<tr>
<td></td>
<td></td>
<td>Cheng et al</td>
<td>2009</td>
<td>Sorafenib</td>
<td>150/76</td>
<td>97/3/0</td>
<td>25/70/5</td>
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<td>Thomas et al</td>
<td>2007</td>
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<td>NR</td>
<td>25 wk</td>
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<tr>
<td></td>
<td>2</td>
<td>Philip et al</td>
<td>2005</td>
<td>Erlotinib</td>
<td>38</td>
<td>71/26/3</td>
<td>26/63/11</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>4–8 wk</td>
<td>NR</td>
<td>13</td>
<td></td>
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<tr>
<td>Sorafenib + erlotinib</td>
<td>3</td>
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<td>2012</td>
<td>Sorafenib + erlotinib</td>
<td>362/358</td>
<td>96/4/0</td>
<td>60/40</td>
<td>13/24</td>
<td>RECIST</td>
<td></td>
<td>6 wk</td>
<td>NR</td>
<td>3.2 vs 4</td>
<td>NS</td>
<td>9.5 vs 8.5</td>
<td>NS</td>
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<td></td>
<td></td>
<td>plus erlotinib vs</td>
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<td>Sorafenib 400 mg orally twice daily + erlotinib 150 mg orally once daily</td>
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<td></td>
<td></td>
<td></td>
<td>sorafenib</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sorafenib 400 mg orally twice daily + erlotinib 150 mg orally once daily plus placebo 150 mg orally once daily</td>
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<td>Linifanib</td>
<td>2</td>
<td>Toh et al</td>
<td>2012</td>
<td>Linifanib</td>
<td>44</td>
<td>86/14/0</td>
<td>52/39/9</td>
<td>NR</td>
<td>Linifanib 0.25 mg/kg orally daily to patients with Child-Pugh class A and every other day to patients with Child-Pugh class B</td>
<td></td>
<td>8 wk</td>
<td>Stop at disease progression</td>
<td>5.4⁴</td>
<td>9.7</td>
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<td></td>
<td>3</td>
<td>Cainap et al</td>
<td>2012</td>
<td>Linifanib vs sorafenib</td>
<td>514/521</td>
<td>95/5/0</td>
<td>66/34</td>
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<td>Linifanib 17.5 mg orally once daily or sorafenib 400 mg orally twice daily</td>
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<td>5.4 vs 4</td>
<td>.001</td>
<td>9.1 vs 9.8</td>
<td>NS</td>
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Table 2. Continued

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<th>Drug</th>
<th>Phase</th>
<th>Author</th>
<th>Year</th>
<th>Drug</th>
<th>n</th>
<th>A/B/C (%)</th>
<th>B/C (%)</th>
<th>Drug scheme</th>
<th>Criteria</th>
<th>Scheme</th>
<th>Time to progression (mo)</th>
<th>P value (mo)</th>
<th>OS P value</th>
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<tr>
<td>Sunitinib</td>
<td>2</td>
<td>Barone et al</td>
<td>2013</td>
<td>Sunitinib</td>
<td>34</td>
<td>79/21/0</td>
<td>62/29/9</td>
<td>Sunitinib 50 mg orally once daily; 4-wk on/2-wk off schedule of 6-wk cycles</td>
<td>12 wk</td>
<td>Stop at disease progression</td>
<td>2.8</td>
<td>5.8</td>
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<td></td>
<td></td>
<td></td>
<td>6 wk until week 18 and every 8 wk thereafter</td>
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<tr>
<td>Koeberle et al</td>
<td>2010</td>
<td>45</td>
<td>87/13/0</td>
<td>47/53/0</td>
<td>Sunitinib 37.5 mg orally once daily</td>
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<tr>
<td>Zhu et al 180</td>
<td>2009</td>
<td>34</td>
<td>97/3</td>
<td>44/56/0</td>
<td>15/85</td>
<td>Sunitinib 37.5 mg orally once daily</td>
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<tr>
<td>Faivre et al 181</td>
<td>2009</td>
<td>37</td>
<td>84/16</td>
<td>51/49</td>
<td>92/5</td>
<td>Sunitinib 50 mg/day orally once daily; 4-wk on/2-wk off schedule of 6-wk cycles</td>
<td>At 4 wk of treatment and then every 6 wk</td>
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<td></td>
<td>5.3</td>
<td>8</td>
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<tr>
<td>Cheng et al 187</td>
<td>2013</td>
<td>530/544</td>
<td>99/1</td>
<td>53/47/0</td>
<td>16/84</td>
<td>Sunitinib 37.5 mg orally once daily or sorafenib 400 mg twice daily</td>
<td>Every 6 wk for the first 24 wk and every 8 wk thereafter</td>
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<td>3.6 vs 3.6 NS</td>
<td>7.9 vs 10.2 NS</td>
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<td>Brivanib</td>
<td>2</td>
<td>Park et al</td>
<td>2011</td>
<td>Brivanib</td>
<td>55</td>
<td>91/9</td>
<td>45/49/5</td>
<td>11/89</td>
<td>Brivanib 800 mg orally once daily Sorafenib 400 mg orally twice daily or brivanib 800 mg orally once daily</td>
<td>Modified WHO criteria mRECIST</td>
<td>6 wk</td>
<td>Treatment could continue beyond radiographic progression</td>
<td>2.8</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>6 wk until week 18 and every 8 wk thereafter</td>
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<td>Johnson et al 189</td>
<td>2013</td>
<td>577/578</td>
<td>92/8/0</td>
<td>61/39/0</td>
<td>92/8</td>
<td>Brivanib 800 mg orally once daily Sorafenib 400 mg orally twice daily or brivanib 800 mg orally once daily</td>
<td>16/84</td>
<td>Sunitinib 37.5 mg orally once daily or sorafenib 400 mg twice daily</td>
<td>Every 6 wk for the first 24 wk and every 8 wk thereafter</td>
<td>4.2 vs 4.1 NS</td>
<td>9.5 vs 9.9 NS</td>
<td></td>
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</table>

a Child–Pugh class A/B/C (%) b BCLC B/C (%) c Criteria Scheme d Treatment discontinuation criteria e Time to progression (mo) f P value (mo) g OS P value h Tumor response
<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Author</th>
<th>Year</th>
<th>Drug</th>
<th>n</th>
<th>Population</th>
<th>Tumor response</th>
<th>Treatment discontinuation criteria</th>
<th>Time to progression (mo)</th>
<th>P value</th>
<th>OS (mo)</th>
<th>P value</th>
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<tbody>
<tr>
<td>FOLFOX-4</td>
<td>2</td>
<td>Qin et al</td>
<td>2012</td>
<td>FOLFOX-4</td>
<td>20</td>
<td>NR</td>
<td>Oxaliplatin 85 mg/m² IV on day 1; calcium folinate 200 mg/m² IV on days 1 and 2; 5-fluorouracil 400 mg/m² followed by continuous IV infusion of 5-fluorouracil on days 1 and 2</td>
<td>RECIST</td>
<td>NR</td>
<td></td>
<td></td>
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<td></td>
<td>3</td>
<td>Qin et al</td>
<td>2013</td>
<td>FOLFOX-4 vs doxorubicin</td>
<td>184/187</td>
<td>NA</td>
<td>Every 6 wk, 1 week during the study treatment phase and every 2 months 1 wk during the follow-up phase at the patients’ respective medical centers</td>
<td>Every 6 wk during the study treatment and every 2 mo during the follow-up phase at the patients’ respective medical centers</td>
<td>Disease progression or eligibility for surgical resection</td>
<td>2.9 vs 1.8</td>
<td>NS</td>
<td>6.4 vs 4.9</td>
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<td>Second line</td>
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<tr>
<td>Brivanib</td>
<td>2</td>
<td>Finn et al</td>
<td>2012</td>
<td>Brivanib</td>
<td>46</td>
<td>91/9</td>
<td>Brivanib 800 mg orally once daily</td>
<td>Modified WHO criteria 6 wk Stop at disease progression</td>
<td>6.6 (mRECIST)</td>
<td>9.8</td>
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<tr>
<td></td>
<td>3</td>
<td>Llovet et al</td>
<td>2013</td>
<td>Brivanib vs placebo</td>
<td>263/132</td>
<td>92/7/1</td>
<td>Brivanib 800 mg orally once daily + BSC or placebo + BSC daily</td>
<td>Initially modified WHO criteria and subsequently mRECIST for HCC per protocol amendment</td>
<td>Treatment could continue beyond radiographic progression</td>
<td>4.2 vs 2.7</td>
<td>.001</td>
<td>9.4 vs 8.2</td>
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<td>Everolimus</td>
<td>3</td>
<td>Zhu et al</td>
<td>2014</td>
<td>Everolimus vs placebo</td>
<td>362/184</td>
<td>NR</td>
<td>Everolimus 7.5 mg orally or placebo daily</td>
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<td>Stop at disease progression</td>
<td>2.9 vs 2.6</td>
<td>NS</td>
<td>7.6 vs 7.3</td>
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<tr>
<td>Ramucirumab</td>
<td>3</td>
<td>Zhu et al</td>
<td>2014</td>
<td>Ramucirumab vs placebo</td>
<td>283/282</td>
<td>NR</td>
<td>Ramucirumab DP (ICM-1121B) 8 mg/kg IV every 2 wk</td>
<td>RECIST</td>
<td>Stop at disease progression</td>
<td>3.5 vs 2.6</td>
<td>&lt;.001</td>
<td>9.2 vs 7.6</td>
</tr>
</tbody>
</table>

**NOTE.** Results with the agents in phase 2 studies is also provided. PS, Performance Status; NR, not reported; WHO, World Health Organization; NS, not significant; IV, intravenous; BSC, best supportive care.

*The information in the phase 3 trials exposes the patients’ data (Child–Pugh class, PS, and BCLC stage) in the sorafenib arm in first-line trials and active drug in second-line trials.

*bThe median TTP radiology.

Modified with permission from Reig et al.82
HCC develops in livers with ongoing or past inflammation, associated with an altered immune profile.\textsuperscript{198} HCCs have abnormal patterns of epigenetic modification, so clinical studies are under way to study these.\textsuperscript{199} Highly specific agents that block kinases and growth factor receptors have been tested in a small number of patients, some selected according to molecular features of the tumor, and several other proposals are under way.\textsuperscript{200} Analyses of data from a study of ramucirumab as a second-line therapy have found activity in patients with increased levels of AFP; further trials are under way in these patients.

There have been many trials of second-line agents after sorafenib; these include novel chemotherapeutic formulations that aim to increase entry of the drug into cells, agents that might replace cellular components, kinase inhibitors (which enrich the population according to c-Met positivity, such as in the trial of tivantinib\textsuperscript{202}), and oncolytic viruses.\textsuperscript{203} The oncolytic and immunotherapeutic vaccinia virus JX-594 can infect tumor cells to generate an anti-tumor immune response and also disrupt the tumor vasculature.\textsuperscript{204} This agent was not found to be effective in a phase 2 trial,\textsuperscript{204} but another trial, with an improved design, has started. Hopefully, some of these efforts will yield positive outcomes and increase the therapeutic options for patients with HCC.

References


New Approaches

There is an active search for agents that are more effective than sorafenib against HCC (see https://clinicaltrials.gov/). Mostly phase 1 and 2 trials but some phase 3 trials have compared other agents as first-line therapies. Agents that block PD1 receptors have been effective against other cancers, and preliminary findings from patients with HCC have been encouraging.\textsuperscript{197} However, 4 to 8 weeks after treatment. Patients present with jaundice, mild ascites, and moderate cholestasis.\textsuperscript{194} In a retrospective study, Salem et al compared the outcomes of patients who did not have portal vein thrombosis or extrahepatic disease and were treated with either TACE or radioembolization.\textsuperscript{195} Survival was not significantly different between the cohorts, whether analyzing the whole cohort or just the intermediate-stage patients. Sangro et al reported a median survival among patients with HCC of BCLC class B with either bilobar disease or more than 5 nodules of 15.4 months and 16.6 months, respectively.\textsuperscript{192} Survival times were even longer in patients who would have been ideal candidates for TACE. Mazzaferrro et al reported a median overall survival of 18 months among patients with intermediate-stage HCC.\textsuperscript{196} Therefore, radioembolization may be an effective approach in patients not eligible for TACE or sorafenib. However, no randomized controlled trials have assessed the survival benefit of radioembolization compared with established treatment, so radioembolization is still considered experimental.\textsuperscript{9,69,144}


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Conflicts of interest
The authors disclose the following: Morris Sherman has received consulting honoraria from Bayer, Daiichi Sankyo, Merck, and Celsion. Jordi Bruix has consulted for for Gilead, Abbvie, Kowa, Bayer, BTG, Arqule, Terumo, BMS, Boehringer Ingelheim, Kowa, Novartis, OSI, Roche and Oxseo. Maria Reig has received consulting honoraria from Bayer.

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