

# Current Management of Hepatocellular Carcinoma

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**Abstract:** Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. Despite efforts for prevention and screening as well as development of new technologies for diagnosis and treatment, the incidence of HCC has doubled, and mortality rates have increased in recent decades. A variety of important risk factors are associated with the development of HCC, with any type of cirrhosis, regardless of etiology, being the major contributor. Hepatitis C virus infection with bridging fibrosis or cirrhosis and hepatitis B virus infection are independent risk factors. The diagnosis of HCC is made without liver biopsy in over 90% of cases. Screening with ultrasound and alpha-fetoprotein (AFP) at 6-month intervals is advised; however, it is not adequate for patients on the orthotopic liver transplantation (OLT) list. Triple-phase computed tomography and/or magnetic resonance imaging are used in combination with the detection of AFP, AFP-L3%, and/or des-gamma-carboxy prothrombin due to their superior sensitivities and specificities. Several treatment modalities are available, but only surgical resection and OLT are curative. OLT is available only for patients who meet or are downstaged into Milan or University of California, San Francisco criteria. Other treatment options include radiofrequency ablation, microwave ablation, percutaneous ethanol injection, transarterial chemoembolization, radioembolization, cryoablation, radiation therapy, stereotactic radiotherapy, systemic chemotherapy, and molecularly targeted therapies. The management of HCC is based on tumor size and location, extrahepatic spread, and underlying liver function. Given the complexity of the disease, patients are often best served in centers with experience in HCC management, where a multidisciplinary approach can take place.

## Keywords

Hepatocellular carcinoma, hepatoma, sorafenib, liver transplantation, radiofrequency ablation, transarterial chemoembolization

**H**epatocellular carcinoma (HCC) is the most common primary liver malignancy. It is the third leading cause of death from cancer worldwide and the ninth leading cause of cancer deaths in the United States.<sup>1</sup> A total of 30,640 new liver and intrahepatic bile

duct cancer cases were estimated to occur in 2013 as well as 21,670 deaths.<sup>2</sup> Overall, liver cancer is more common in men than women, with a ratio of 2.4:1.<sup>1</sup> Regions of high incidence consist of Eastern and Southeastern Asia, Middle and Western Africa, Melanesia, and Micronesia/Polynesia, with lower rates in developed regions.<sup>3</sup> However, incidence and mortality patterns are changing.<sup>4</sup>

In recent decades in the United States, the incidence of HCC has doubled, and HCC mortality rates have increased. The estimated 5-year survival rate for HCC is less than 12%, making HCC one of the faster-growing causes of death in the United States.<sup>5,6</sup> A US population-based study found that the incidence of HCC was highest among Asians, nearly double that of white Hispanics, and 4 times higher than that of the non-Hispanic white population.<sup>7</sup> Attempts to prevent HCC should focus on preventing infection with hepatitis B virus (HBV) and hepatitis C virus (HCV), treating patients with viral hepatitis who are candidates for treatment, avoiding environmental toxins, encouraging cessation of heavy alcohol use, and removing excess iron from patients with hereditary hemochromatosis.

A variety of important risk factors are associated with the development of HCC. The prevalence of cirrhosis in persons with HCC is approximately 80% in autopsied series worldwide.<sup>8</sup> Dual infection with HCV or HBV in cirrhotic patients has been linked to an increased risk of HCC. HBV infection is unique in that it can lead to development of HCC even in the absence of cirrhosis. The annual incidence of HCC in HBV carriers was 0.5% in a prospective controlled study.<sup>9</sup> The incidence of HCC in patients with known cirrhosis is 2.5% per year,<sup>10</sup> with a 5-year cumulative HCC risk of 15% in areas with high HBV prevalence and 10% in the West.<sup>11</sup> HCV infection accounts for at least one-third of HCC cases in the United States,<sup>12</sup> and the overall HCC risk in patients with HCV infection and cirrhosis is 2% to 8% per year.<sup>10</sup>

In patients infected with HCV, the incidence of HCC increases as the stage of fibrosis progresses, from 0.5% in stage F0 or F1 fibrosis to 7.9% in stage F4 fibrosis in one series from Japan.<sup>13</sup> The transition from bridging fibrosis to cirrhosis cannot be determined clinically. It has been suggested that the incidence of HCC in HCV-associated cirrhosis only increases substantially once the platelet count is lower than 100/L to 109/L<sup>14</sup> regardless of liver function. Although some hepatology societies advocate for surveillance of HCC in patients with identified bridging fibrosis, others find it controversial.<sup>10</sup> Viral load and genotype do not appear to influence progression to HCC in HCV-related cirrhosis.

Several studies have evaluated the impact of treatment for chronic HBV and HCV infections on the risk of HCC; one study reported that antiviral therapy reduced the 5-year

cumulative incidence of HCC by 7.8% in patients with HCV infection and by 7.1% in those with HBV infection.<sup>15</sup> For patients infected with HCV, the effect is particularly relevant among patients achieving a sustained virologic response<sup>16</sup>; however, those patients continue to require screening and surveillance. Synergy between alcohol intake and HCV/HBV infection also has been observed. The risk of liver cancer is increased approximately 2- to 4-fold among persons drinking more than 60 to 80 g/day of alcohol.<sup>17</sup>

Patients usually have no symptoms other than those related to their chronic liver disease. Suspicion of HCC should be heightened in patients with previously compensated cirrhosis in whom decompensation develops, as this is often associated with extension of the tumor into the hepatic or portal vein or arteriovenous shunting induced by the tumor.<sup>18</sup> Extrahepatic spread is present at the time of diagnosis in up to 15% of cases. The most common sites, in order, are the lung, intra-abdominal lymph nodes, bone, and adrenal glands.<sup>19</sup>

## Diagnosis and Surveillance

### *Surveillance Is Crucial*

Surveillance is key because patients at high risk who are screened for HCC receive a diagnosis at an earlier stage compared with those who are not screened. Patients who receive an early diagnosis consequently have more treatment options and a better prognosis. A randomized controlled trial indicated that biannual screening reduced HCC mortality by 37%.<sup>20</sup>

### *Who Should Be Screened?*

The American Association for the Study of Liver Diseases (AASLD) guidelines, updated in 2010, suggest surveillance of high-risk patient groups,<sup>10,21</sup> which include: 1) HBV carriers who are Asian men older than age 40 years, Asian women older than age 50 years, cirrhotics, Africans, African Americans, and those with a family history of HCC (for whom surveillance should start at age <40 years) and 2) all patients with cirrhosis. The AASLD recommends surveillance for patients receiving treatment for HBV infection, even if they have cleared the virus. Liver disease is also more rapidly progressive in patients who are coinfecting with HIV and either HBV or HCV.<sup>22-24</sup> The criteria for entering coinfecting patients into programs for HCC screening are the same as for monoinfected patients.

### *Screening Modalities*

The available modalities for HCC screening include both serologic markers and radiographic tests. The imaging tests most commonly used for the diagnosis of HCC include ultrasonography (US), multiphase computed tomography (CT), and magnetic resonance imaging (MRI) with contrast.

On CT and MRI, typical HCC lesions display increased arterialization as well as decreased presence of contrast agents compared with the surrounding liver during portal vein and/or equilibrium phase imaging.<sup>24</sup> The 2010 AASLD guidelines recommend that surveillance be performed using US at 6-month intervals.<sup>10,21</sup> However, CT or MRI is preferred in patients in whom US is not adequate because of technical reasons or because the patient is on the orthotopic liver transplantation (OLT) waiting list.<sup>25</sup> A retrospective analysis of the abilities of the different imaging modalities to detect HCC demonstrated superior sensitivities with CT and MRI in comparison with US, especially for small lesions.<sup>26</sup> (Overall sensitivities of US, CT, and MRI were 46%, 65%, and 72%, respectively.)

Although serum alpha-fetoprotein (AFP) is often elevated in patients with HCC, its sensitivity and specificity were estimated at 41% to 65% and 80% to 94%, respectively, in one study.<sup>27</sup> It is generally accepted that serum levels greater than 500 µ/L in high-risk patients are diagnostic for HCC.<sup>28</sup> However, negative values do not rule out HCC. AFP also may be elevated in patients with chronic liver disease in the absence of cancer (especially with inflammation), in pregnancy, tumors of gonadal origin, and a variety of other malignancies. Because of the limitations of serum AFP measurements, several other serum markers of HCC used alone or in combination with AFP have been evaluated.

AFP-L3%, which is the ratio of AFP-L3 to total AFP, is a fucosylated fraction of AFP that may be helpful in patients with low serum AFP levels<sup>29,30</sup> and for early detection of HCC.<sup>31</sup> Studies comparing AFP-L3% with AFP alone have failed to demonstrate significantly improved sensitivity for HCC diagnosis, but high specificities associated with AFP-L3% suggest that this ratio may be useful in improving risk stratification when used in combination with total AFP levels.<sup>32-34</sup> Des-gamma-carboxy prothrombin (DCP), an abnormal form of prothrombin, also has shown promise in the diagnosis of HCC, but it cannot be used in patients on warfarin, as warfarin causes an elevation of this test in the absence of malignancy. Some studies have shown that DCP was significantly better than total AFP or AFP-L3% in differentiating HCC from cirrhosis,<sup>35</sup> whereas other studies have stated that the combination of DCP with AFP has higher sensitivity and specificity than either one alone.<sup>36</sup>

Currently, AFP-L3% and DCP are not recommended by the AASLD. The guiding principle should be to use the best available surveillance test regularly; as a result, strategies such as alternating AFP and US at intervals have no basis.<sup>10,21</sup> The combined use of AFP and US results in a relatively small increase in detection rates, but it also increases costs and false-positive rates<sup>37</sup> and is not recommended by the AASLD. Other societies

**Table 1.** HCC Surveillance Guidelines for High-Risk Patients

Society/Institution	Guidelines
American Association for the Study of Liver Diseases <sup>10,21</sup>	US every 6 months
European Association for the Study of the Liver <sup>39</sup>	US every 6 months
Asian-Pacific Association for the Study of the Liver <sup>38</sup>	AFP + US every 6 months
National Comprehensive Cancer Network <sup>40</sup>	AFP + US every 6-12 months
US Department of Veterans Affairs <sup>41</sup>	AFP + US every 6-12 months

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; US, ultrasonography.

recommend using a combination of US and AFP at 6- to 12-month intervals<sup>38-41</sup> (Table 1).

A mass found incidentally or through screening in the setting of a patient with known HBV-associated cirrhosis or cirrhosis of another etiology is likely to be HCC. Nodules that are smaller than 1 cm are often not HCC; they should be followed with US at intervals of 3 to 6 months until proven to be stable or they disappear, and if there has been no growth over a period of up to 2 years, the patient can revert to routine surveillance.

Lesions larger than 1 cm in diameter should be evaluated with CT or MRI. If the appearance is typical for HCC, no further investigation is required, but if the characteristics are not typical for HCC, either a second study or a biopsy can be performed. However, the diagnosis of HCC is made without biopsy in over 90% of cases. If the biopsy is negative for HCC, patients should be followed by imaging at 3- to 6-month intervals until the nodule disappears, enlarges, or displays diagnostic characteristics of HCC. If the lesion enlarges but remains atypical for HCC, a repeat biopsy is recommended. It is important to be aware that biopsies are not completely harmless. One study reported a sensitivity and specificity of 91.5% and 100.0%, respectively, as well as a 0.4% rate of bleeding (5 of the 11 patients who bled died) and 0.2% rate of implantation metastases.<sup>42</sup>

## Staging

The severity of underlying liver disease, the size of the tumor, the extension of the tumor into adjacent structures, and the presence of metastases are important determinants of survival. The 4 most commonly used systems for staging and prognosis of HCC are the Tumor, Node, Metastasis (TNM) system, the Okuda system, the Barcelona Clinic Liver Cancer (BCLC) system, and the prognostic staging system for HCC (CLIP score). There is no consensus as

to which staging system is best in predicting the survival of patients with HCC.<sup>43</sup> The consensus statement of the American Hepato-Pancreato-Biliary Association, updated in 2010, recommends the use of the TNM system to predict outcomes following resection or liver transplantation and the BCLC scheme for patients with advanced HCC who are not candidates for surgery.<sup>44</sup> BCLC staging classification is comprised of 4 stages that are based on the extent of the primary lesion, performance status, presence of constitutional symptoms, vascular invasion, extrahepatic spread, and Okuda stage.<sup>45</sup> Early-stage (A) patients are asymptomatic and have tumors that are suitable for radical therapies; intermediate-stage (B) patients are asymptomatic and have multinodular HCC; advanced-stage (C) patients have symptomatic tumors, vascular invasion, and/or extrahepatic spread; and patients with stage D disease have either Okuda stage III tumors or an Eastern Cooperative Oncology Group performance status of 3 or 4. Okuda staging includes tumor size, ascites, serum albumin, and jaundice as measures of the severity of cirrhosis.<sup>46</sup>

## Treatment

HCC can be treated curatively with surgical resection or liver transplantation if diagnosed at an early stage; however, since most patients with HCC present with advanced disease and underlying liver dysfunction, only 15% are eligible for curative treatments,<sup>47</sup> and they generally have a poor prognosis with median survival times of less than 1 year.<sup>48</sup> Several other treatment modalities are available, including radiofrequency ablation (RFA), microwave ablation, percutaneous ethanol injection (PEI), transarterial chemoembolization (TACE), radioembolization, cryoablation, radiation therapy, stereotactic radiotherapy, systemic chemotherapy, and molecularly targeted therapies (eg, sorafenib [Nexavar, Bayer/Onyx]). A comparison of recurrence and survival among different treatment modalities is shown in Table 2.

The BCLC staging classification provides stratification of patients to set their prognosis and guide treatment strategies through a well-defined schedule.<sup>45</sup> The Figure depicts suggested management of HCC based on BCLC, Milan criteria, and Child-Pugh classification; in addition, it includes newer treatment modalities not included on the original BCLC algorithm, such as sorafenib and yttrium-90 (Y90), and introduces the concept of downstaging.

### Tumor Resection

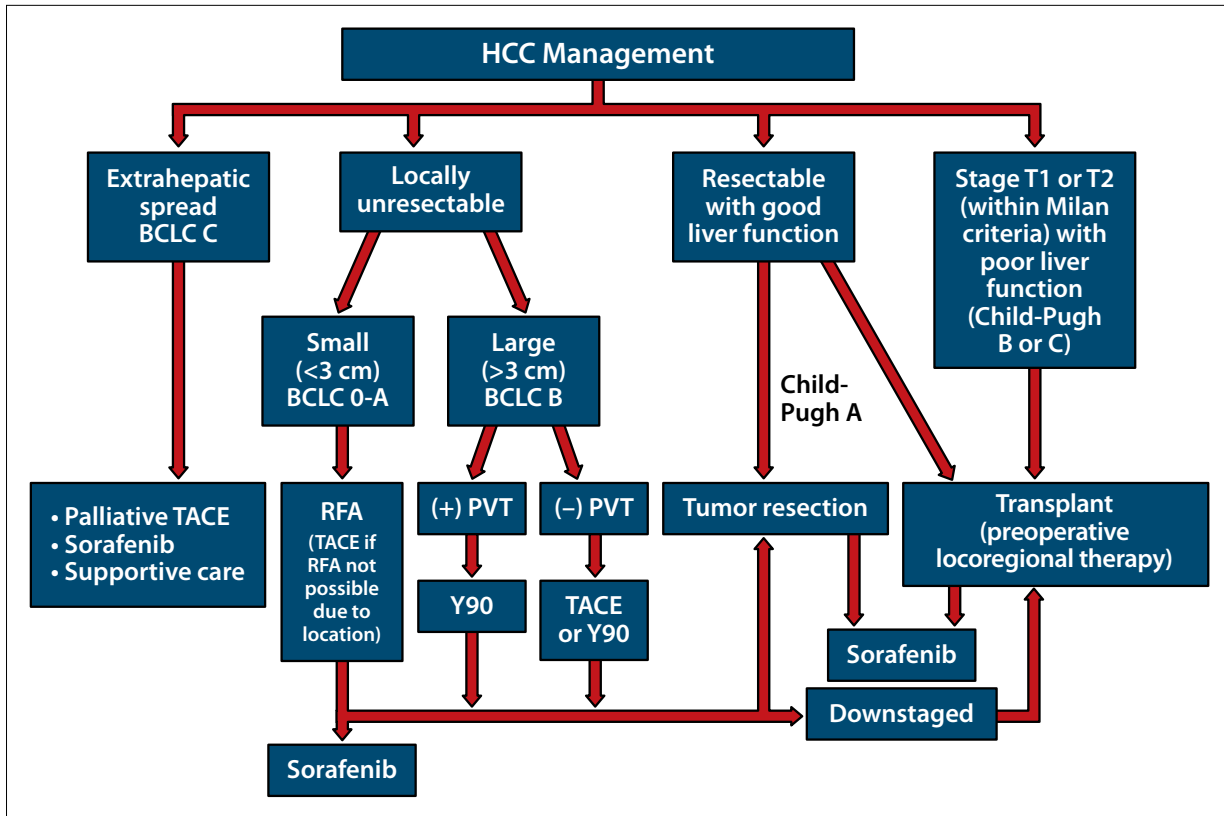
The assessment of potential resectability of HCC focuses on whether the tumor is confined to the liver, its size and location, and whether the underlying liver function will allow resection without increasing morbidity and mor-

**Table 2.** Treatment Modalities for Hepatocellular Carcinoma

Treatment Modality	Survival	Recurrence
Hepatectomy	41%-74% (5 yrs) <sup>50</sup>	70% (5 yrs) <sup>25,33</sup>
OLT	>70% (5 yrs) <sup>10,21,39,57</sup>	<15% (5 yrs) <sup>10,21,39,57</sup>
RFA/PEI	70% (5 yrs) <sup>33,68</sup> lesions <2 cm	2%-50% (3 yrs) <sup>73,74</sup>
TACE/Y90	20%-60% (2 yrs) <sup>77</sup>	TACE is a noncurative treatment; response rates, 6% to 60% <sup>77</sup>
Sorafenib	Median survival is 3 months longer than with placebo <sup>86</sup>	Time to progression is 3 months longer than with placebo <sup>86</sup>

OLT, orthotopic liver transplantation; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; Y90, yttrium-90.

tality. Resection is considered the first-line treatment for patients with solitary tumors confined to the liver without radiographic evidence of invasion of the vasculature and preserved liver function (normal bilirubin and either hepatic venous pressure gradient  $\leq 10$  mmHg, platelet count  $>100,000$ , or no varices at endoscopy).<sup>33,49</sup> Post-resection 5-year survival rates are as high as 41% to 74% in this population.<sup>50</sup> Resection also can be performed for multifocal HCC inside Milan criteria or in the case of mild portal hypertension when patients are not suitable for OLT,<sup>51</sup> although whether such patients could benefit from other locoregional therapies, avoiding the risk of surgery and liver decompensation after surgery, has been debated. In fact, perioperative mortality in cirrhotics after HCC resection is approximately 2% to 3%,<sup>33</sup> which, as expected, is greater than for noncirrhotics. As a general rule, patients who have complications of cirrhosis (such as bleeding, ascites, or marked portal hypertension) have insufficient hepatic reserve to withstand a partial hepatectomy. Although many surgeons restrict eligibility for resection to patients with tumors that are 5 cm or smaller in diameter, there is no general rule regarding tumor size for selection of patients for resection,<sup>52,53</sup> even though the risk of vascular invasion and dissemination increases with tumor size. Another factor that affects the decision to pursue local resection is the risk of postresection tumor recurrence. Recurrence rates may be as high as 70% after 5 years.<sup>25,33</sup> De novo tumor development can occur following resection, but the majority of HCC recurrences within 1 to 2 years are secondary to dissemination from the primary tumor. Although the best approach to postresection tumor recurrence has not been well studied, repeat resection



**Figure.** An algorithm for the management of HCC.

BCLC 0-A, Barcelona Clinic Liver Cancer stage 0 to early stage; BCLC B, Barcelona Clinic Liver Cancer immediate stage; BCLC C, Barcelona Clinic Liver Cancer advanced stage; HCC, hepatocellular carcinoma; PVT, portal vein thrombosis; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; Y90, yttrium-90.

is rarely ideal. Instead, salvage liver transplantation or other locoregional therapies, with or without oral multi-kinase inhibitors, may be more suitable.<sup>50</sup>

### Liver Transplantation

Among patients with unresectable disease, the most viable surgical option is often liver transplantation, frequently in conjunction with adjuvant therapy such as TACE or percutaneous ablation.<sup>54,55</sup> However, liver transplantation is not appropriate for all patients, and thorough evaluation is necessary to prudently allocate the scarce resources available.<sup>33</sup> In 1996, Mazzaferro and colleagues published a landmark prospective study involving less than 50 patients who were transplanted for HCC under predefined criteria (single HCC  $\leq 5$  cm or 3 HCC  $\leq 3$  cm each), known as the Milan criteria, and showed a 4-year survival of 75%.<sup>56</sup> This established deceased-donor liver transplantation as a viable option for the treatment of HCC. Subsequent experiences of OLT for HCC inside the Milan criteria confirmed a survival rate exceeding 70% at 5 years, with recurrence in less than 15%.<sup>10,21,39,57</sup> These outcomes are also similar to expected survival rates for patients undergoing transplantation for cirrhosis without HCC.<sup>58</sup>

Several studies have investigated the effect of expanding the Milan criteria, primarily by liberalizing the restrictions on tumor size. The University of California, San Francisco criteria, which include a single nodule of 6.5 cm or greater or 2 to 3 nodules of 4.5 cm or greater and a total diameter of 8 cm or greater, have been studied retrospectively and prospectively and have shown survival and recurrence rates equal to those of persons transplanted using the Milan criteria.<sup>33</sup> Nevertheless, national and international guidelines still indicate OLT for HCC inside Milan criteria while awaiting further data to support expansion of the criteria.<sup>10,21,39,57</sup>

Recent interest has focused on the use of a downstaging approach in which patients with HCC exceeding transplantation criteria are treated with locoregional therapy (ie, TACE and/or ablation therapy) to decrease the tumor burden to the point of meeting transplantation criteria.<sup>59-61</sup> The data are conflicting. Some experts suggest offering OLT to patients who achieve effective downstaging, while others favor OLT as a rescue treatment in patients who do not achieve an effective response.<sup>62,63</sup> Yao and colleagues published a downstaging protocol using TACE and/or RFA and have shown survival rates



of 96.2% at 1 year and 92.1% at 4 years among patients who received transplants.<sup>61</sup>

The downstaging approach is also controversial. Some experts believe that large or multifocal tumors retain the same risk of recurrence despite successful downstaging and fear that increasing the pool of potential transplant recipients may contribute to longer wait-list times, higher dropout rates, and greater wait-list mortality.<sup>33</sup>

A major disadvantage of OLT is the long waiting time for donor organs. Under the current United Network for Organ Sharing policy, patients with HCC within the Milan criteria receive Model for End-Stage Liver Disease scores that begin at 22 and increase in a stepwise fashion (equivalent to an additional 10% increase in candidate mortality) every 3 months after the results of repeat imaging with either CT or MRI have confirmed that criteria are still met.<sup>64</sup> As a result, patients with HCC in some areas of the country may wait more than 2 years before being offered a liver graft. Living donor liver transplant (LDLT) is an alternative option; however, there is a donor risk of death of approximately 0.3% and of life-threatening complications of approximately 2%. For this reason, LDLT should be restricted to centers of excellence.<sup>25</sup> Data are still forthcoming as to whether LDLT offers the same survival as deceased donor liver transplant in patients with HCC.

## Nonsurgical Therapies for Localized Hepatocellular Carcinoma

### *Percutaneous Local Ablation: Radiofrequency Ablation and Percutaneous Ethanol Injection*

Percutaneous local ablation, which includes RFA and PEI, is the standard of care for BCLC stage 0-A not suitable for surgery. RFA relies on a needle electrode to deliver a high-frequency alternating current, resulting in frictional heating of the tissue and subsequent necrosis.<sup>65</sup> Injection of 95% ethanol directly into a tumor through a needle can induce local coagulation necrosis and a fibrous reaction, as well as thrombosis of tumor microvasculature and tissue ischemia.<sup>66</sup> In tumors 3 cm or larger, both RFA and PEI achieve complete necrosis in 80% to 90%,<sup>67</sup> making percutaneous local ablation competitive with resection.<sup>68</sup>

Before the advent of RFA, PEI was the most widely accepted, minimally invasive method for treating such patients. However, RFA continues to demonstrate the most predictable efficacy in both small and large tumors, and studies suggest that patients treated with RFA have superior survival and local recurrence-free rates compared with those of PEI.<sup>69,70</sup> Although there is no absolute tumor size beyond which RFA should not be considered, the best outcomes are in patients with a single tumor that is less than 4 cm in diameter or in patients who have no more

than 3 HCC nodules, none measuring more than 3 cm in greatest dimension.<sup>71</sup> RFA is also used for treating recurrent HCC in the liver following partial hepatectomy.<sup>72</sup> Local recurrence rates for RFA and PEI are variable, ranging from 2% to 50% up to 3 years after treatment.<sup>73,74</sup> Some studies demonstrate 5-year survival rates of 70% among patients with tumors less than 2 cm.<sup>33,68</sup>

### *Transarterial Chemoembolization*

Among patients with large multifocal HCC or those whose tumor characteristics are not appropriate for surgical or ablative therapy, TACE is recommended as a first-line, noncurative treatment for BCLC stage B multinodular asymptomatic tumors without vascular invasion or extrahepatic spread.<sup>25,75</sup> The observation that the majority of the blood supply to HCC is derived from the hepatic artery, rather than the portal vein, has led to the development of techniques designed to eliminate the tumor's blood supply or administer cytotoxic chemotherapy directly to the tumor. In a systematic review, it was determined that TACE induced extensive tumor necrosis in more than 50% of patients, and, according to conventional World Health Organization criteria, the reported rate of objective response ranges between 16% and 60%.<sup>76</sup> TACE involves the injection of a chemotherapeutic agent that is mixed with embolic material and administered selectively into the feeding arteries of the tumor to potentially obtain higher intratumoral drug concentrations compared with intravenous therapy, with occlusion of the blood vessel causing infarction and necrosis.<sup>76</sup>

The choice of chemotherapeutic agent is not standardized, but a variety of agents have been used, including doxorubicin, cisplatin, mitomycin, and epirubicin. The use of embolic, drug-eluting microspheres offers a promising alternative that has nearly replaced conventional TACE at many institutions. In a recent multicenter, phase 2, prospective, randomized, clinical trial, doxorubicin-eluting beads demonstrated a trend toward higher treatment response rates and increased tumor necrosis compared with conventional TACE.<sup>76</sup>

Much research has been conducted on TACE, and given the variety of study designs, patient characteristics, and specific TACE methods used, estimating survival and recurrence rates is challenging. The improvement in survival in treated patients may range from 20% to 60% at 2 years.<sup>77</sup> Nevertheless, it is clear that the relevance of the improvement compared with the outcome if untreated is largely dependent on the patient's baseline characteristics regarding tumor stage, liver function, and general health status.<sup>10</sup> Absolute contraindications to TACE include main portal vein thrombosis, severe encephalopathy, biliary obstruction, and Child-Pugh C cirrhosis. TACE causes some degree of ischemic hepatic damage, which has the potential to lead to

hepatic decompensation, with a rate of up to 20% in one series.<sup>78</sup> However, the most common adverse effect of TACE is postembolization syndrome, which occurs in 60% to 80% of patients. This consists of varying degrees of right upper quadrant pain, nausea, a moderate degree of ileus, fatigue, fever, and transient elevation of aspartate aminotransferase, alanine aminotransferase, and bilirubin values. Symptoms are usually self-limited, lasting 3 to 4 days; full recovery is typical within 7 to 10 days.

#### ***Yttrium-90–Labeled Microspheres Radioembolization***

An alternative means of delivering focal radiotherapy uses radioactive isotope Y90-labeled microspheres and selectively delivers them to the tumor via the hepatic artery.<sup>79</sup> This technique has the major advantage of being indicated in the case of portal vein neoplastic thrombosis, which is one of the major contraindications for TACE,<sup>80</sup> and its toxicities have proven to be well tolerated.<sup>81</sup> However, Y90 is contraindicated in patients with significant hepatopulmonary shunting because it could result in very high levels of pulmonary radiation exposure.<sup>5</sup> Tumor necrosis and survival depend on the tumor risk and Child-Pugh scoring systems, but response rates are similar to those obtained with TACE.<sup>82,83</sup> The 2010 Clinical Practice Guidelines from the AASLD state that radioembolization cannot be recommended as standard therapy for advanced HCC outside of clinical trials, although in many areas of the country, Y90 has become a standard treatment for HCC in some cases when other locoregional therapies are not appropriate.

#### ***Systemic Therapy***

Systemic therapies examined in the past, including both cytotoxic and hormonal agents, have provided limited or no benefit for patients with HCC.<sup>84</sup> In 2007, the tyrosine kinase inhibitor (TKI) sorafenib was approved for use in advanced HCC based on an improvement in survival compared with placebo.<sup>85,86</sup> Despite initial responses to sorafenib, most patients with HCC experience a loss of efficacy, which may be due to “resistance” via escape/compensatory mechanisms.<sup>87</sup> In addition, 20% to 38% of patients discontinue its use due to adverse effects. As with other TKIs, sorafenib also has had class adverse effects, including skin-related toxicities, hypertension, proteinuria, diarrhea, and cytopenias as well as life-threatening complications, such as thromboembolism, bleeding, and bowel perforation.<sup>88-90</sup> Liver failure also has been reported more frequently in patients whose liver disease is Child-Pugh stage B/C.<sup>91</sup>

The mainstay of palliative therapy for advanced HCC is sorafenib, which is indicated strictly in advanced HCC (BCLC stage C) or HCC progressing after surgical or locoregional therapies in patients with well-preserved

liver function and good performance status.<sup>25</sup> Studies are ongoing to determine the role of sorafenib as adjuvant therapy with surgical or locoregional therapy. Determining efficacy and safety in the substantial portion of patients with advanced HCC remains a challenge.<sup>87</sup> Other TKIs are in development to treat HCC, both in the first-line setting and for use following sorafenib failure. Agents with antiangiogenic properties in phase 2 and 3 development for the treatment of patients with HCC include bevacizumab (Avastin, Genentech), ramucirumab, ABT-869, everolimus, and ARQ 197.<sup>87</sup>

#### **Conclusion**

HCC is a rapidly growing cause of morbidity and mortality in the United States. Although HCC can be a devastating disease, the best chance for prolonged survival is to screen and diagnose early. Hepatology societies differ in their preferred methods of surveillance, but, in general, US with or without AFP every 6 months is adequate for most patients. Multiple treatment modalities are available, and research on newer options is underway. Given the complexity of the disease, patients are often best served in centers with experience in HCC management, where a multidisciplinary approach can take place. Advances in HCC prevention, early detection, and treatments have resulted in improved survival and prognosis for a disease that a few decades ago was considered a death sentence.

*Dr Crissien has no relevant conflicts of interest to disclose. Dr Frenette serves on the speakers bureau for Bayer/Onyx Pharmaceuticals.*

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