# **Hepatobiliary Cancers, Version 2.2021**

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## **ABSTRACT**

The NCCN Guidelines for Hepatobiliary Cancers focus on the screening, diagnosis, staging, treatment, and management of hepatocellular carcinoma (HCC), gallbladder cancer, and cancer of the bile ducts (intrahepatic and extrahepatic cholangiocarcinoma). Due to the multiple modalities that can be used to treat the disease and the complications that can arise from comorbid liver dysfunction, a multidisciplinary evaluation is essential for determining an optimal treatment strategy. A multidisciplinary team should include hepatologists, diagnostic radiologists, interventional radiologists, surgeons, medical oncologists, and pathologists with hepatobiliary cancer expertise. In addition to surgery, transplant, and intra-arterial therapies, there have been great advances in the systemic treatment of HCC. Until recently, sorafenib was the only systemic therapy option for patients with advanced HCC. In 2020, the combination of atezolizumab and bevacizumab became the first regimen to show superior survival to sorafenib, gaining it FDA approval as a new frontline standard regimen for unresectable or metastatic HCC. This article discusses the NCCN Guidelines recommendations for HCC.

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**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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The complete NCCN Guidelines for Hepatobiliary Cancers are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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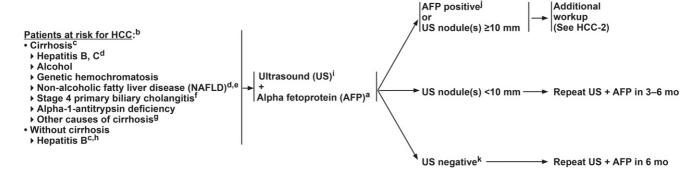
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Individual disclosures for the NCCN Hepatobiliary Cancers Panel members can be found on page 565. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

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<sup>\*</sup>Discussion Writing Committee Member.

#### HEPATOCELLULAR CARCINOMA (HCC) SCREENING<sup>a</sup>



<sup>\*</sup>Available online, in these guidelines, at NCCN.org

c Patients with cirrhosis or chronic hepatitis B viral infection should be enrolled in an HCC screening program (See Discussion)

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HCC-1

## **Overview**

Incidence and mortality rates for most cancers are declining; however, the incidence and mortality rates for liver cancer are increasing. 1-5 The major risk factors for the development of hepatocellular carcinoma (HCC) are cirrhosis and chronic liver disease, regardless of etiology.<sup>6,7</sup> Specific risk factors include viral infections caused by hepatitis B virus (HBV) and/or hepatitis C virus (HCV), chronic alcohol consumption, particular comorbidities or other conditions such as non-alcoholic fatty liver disease, nonalcoholic steatohepatitis, genetic hemochromatosis, coinfection with HBV/HCV, and HIV. 1,8-14 Localized HCC is asymptomatic for much of its natural history. Nonspecific symptoms associated with more advanced HCC can include jaundice, anorexia, weight loss, malaise, and upper abdominal pain. Physical signs of HCC can include hepatomegaly and ascites.<sup>15</sup> Common sites of HCC metastasis include the lung, adrenal glands, peritoneum, and bone. 16,17 The majority of patients diagnosed with HCC have advanced disease, and only a small percentage are eligible for potentially curative therapies. It is essential that all patients be evaluated by a multidisciplinary team prior to initiation of treatment. Careful patient selection for treatment and patient engagement are essential.

## **Screening for HCC**

The panel supports the recommendation by the American Association for the Study of Liver Diseases (AASLD) that HCC screening in patients with risk factors for HCC should consist of a program including standardized screening tests, recall procedures, and quality control procedures in place.<sup>18</sup> The AASLD and the European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer recommend that ultrasound (US) screening in at-risk patients be done every 6 months. 3,18,19

Support for enrolling individuals at high risk for HCC in a screening program comes from a large randomized controlled trial (RCT) in China of 18,816 men and women with HBV infection or a history of chronic hepatitis, defined as patients with abnormalities on serum liver tests lasting for 6 months or more. In this study, screening with serum alpha-fetoprotein (AFP) testing and liver ultrasound every 6 months was shown to result in a 37% reduction in HCC mortality, despite the fact that less than 60% of individuals in the screening arm completed the screening program.20 HCC screening should be performed in at-risk populations regardless of age.

AFP and liver US are the most widely used methods of screening for HCC.21 A review of serum protein

<sup>&</sup>lt;sup>a</sup> See Principles of Imaging (HCC-A\*).

<sup>&</sup>lt;sup>b</sup> Adapted with permission from Marrero JA, et al. Hepatology 2018;68:723-750

d There is evidence suggesting improved outcomes for patients with HCC in the setting of NAFLD/HBV/HCV cirrhosis when the NAFLD/HBV/HCV is successfully treated. Referral to a hepatologist should be considered for the management of these patients. e White DL, Clin Gastroenterol Hepatol 2012;10:1342-1359.

f Beuers U, et al. Am J Gastroenterol 2015;110:1536-1538.

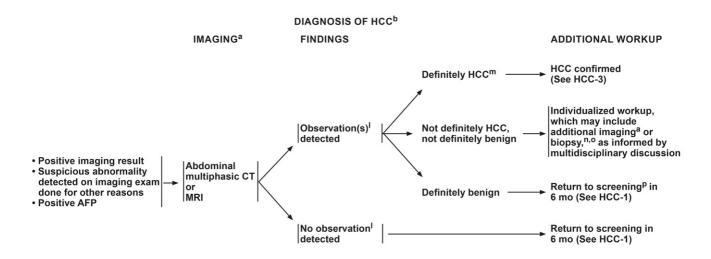
<sup>9</sup> Schiff ER, Sorrell MF, and Maddrey WC. Schiff's Diseases of the Liver. Philadelphia: Lippincott Williams & Wilkins (LWW); 2007.

h Additional risk factors include HBV carrier with family history of HCC, Asian males ≥40 y, Asian females ≥50 y, and African/North American Blacks with hepatitis B.

Most clinical practice guidelines recommend US for HCC screening. US exams should be done by qualified sonographers or physicians. Liver dynamic CT or dynamic MRI may be performed as an alternative to US if US fails to detect nodules or if visualization is poor. Korean Liver Cancer Association; National Cancer Center. Gut Liver 2019;13:227-299. (See Principles of Imaging, HCC-A\*)

Positive or rising AFP should prompt CT or MRI regardness of US results

kUS negative means no observation or only definitely benign observation(s)



<sup>a</sup> See Principles of Imaging (HCC-A\*).

An observation is an area identified at imaging that is distinctive from background liver. It may be a mass or a pseudo lesion.

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HCC-2

biomarkers for early detection of HCC showed that an AFP cut-off value of 100 ng/mL was associated with high specificity (99%) but low sensitivity (31%).<sup>22</sup> In a screening study involving a large population of patients in China infected with HBV or those with chronic hepatitis, and using an AFP cut-off of >20 ng/mL, the detection rate, false-positive rate, and positive predictive value with AFP alone were 69%, 5.0%, and 3.3%; with US alone, they were 84%, 2.9%, and 6.6%; and with the combination of AFP and US, they were 92%, 7.5%, and 3.0%.<sup>23</sup> These results demonstrate that US combined with AFP is a better modality for HCC screening than AFP testing alone. A study of 333 patients with HCC and HBV/HCV determined that patients with HCC diagnosed after surveillance with US and AFP had significantly longer overall survival (OS) and disease-free survival (DFS), compared with patients who had no surveillance prior to diagnosis.<sup>24</sup> Nevertheless, since US is highly operator dependent, the addition of AFP may increase the likelihood of detecting HCC in a screening setting. However, AFP is frequently normal in patients with early-stage disease and its utility as a screening biomarker is limited.<sup>25–27</sup> A recent meta-analysis including 32 studies with 13,367 patients with cirrhosis who were screened for HCC showed that US with AFP improves

sensitivity for detection of HCC, compared with US alone (97% vs 78%, respectively; relative risk [RR], 0.88; 95% CI, 0.83–0.93). Due to the low cost and ease of use, AFP may have utility for enhancing detection of HCC when used in combination with US for screening at-risk individuals. A progressive elevation rate of  $\geq$ 7 ng/mL per month may be more useful as a diagnostic tool for HCC, relative to use of a fixed cut point such as 200 ng/mL.<sup>29</sup>

In these guidelines, the populations considered to be "at risk" for HCC and likely to benefit from participation in an HCC screening program include patients with liver cirrhosis induced by viral (hepatitis B and C) and nonviral causes of cirrhosis (ie, alcoholic cirrhosis, GH, nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, stage IV primary biliary cholangitis, alpha-1 antitrypsin deficiency) and hepatitis B carriers without cirrhosis, regardless of cause.

The panel recommends screening with US and AFP testing (every 6 months) for patients with established risk factors for HCC. Additional imaging (abdominal multiphasic CT or MRI) is recommended in the setting of a rising serum AFP or following identification of a liver mass nodule  $\geq 10$  mm on US, based on AASLD and Liver Imaging Reporting and Data System (LI-RADS) guidelines.<sup>3,30</sup> It

<sup>&</sup>lt;sup>b</sup> Adapted with permission from Marrero JA, Kulik LM, Sirlin C, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2018;68:723-750.

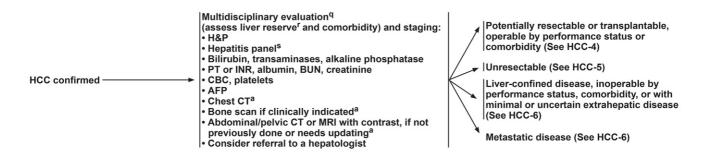
<sup>&</sup>lt;sup>m</sup> Criteria for observations that are definitely HCC have been proposed by LI-RADS and adopted by AASLD. These criteria apply only to patients at high risk for HCC. OPTN has proposed imaging criteria for HCC applicable in candidates for liver transplant. See Principles of Imaging (HCC-A\*).

n Before biopsy, evaluate if patient is a resection or transplant candidate. If patient is a potential transplant candidate, consider referral to transplant center before biopsy. See Principles of Biopsy (HCC-B\*).

P If no observations are detected at diagnostic imaging despite positive surveillance tests, then return to surveillance in 6 months if the most reasonable explanation is that surveillance tests were false positive. Consider imaging with an alternative method +/- AFP if there is reasonable suspicion that the diagnostic imaging test was false negative.

#### **CLINICAL PRESENTATION**

WORKUP



Hepatitis B surface antibody (for vaccine evaluation only).

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HCC-3

is also reasonable to screen patients with cross-sectional imaging (CT or MRI), and this may be commonly used, though not well-studied, in the United States. Cost and availability limit the widespread use of screening using cross-sectional imaging. Liver masses <10 mm are difficult to definitively characterize through imaging. If nodules of this size are found, then US and AFP testing should be repeated in 3 to 6 months.

## **Diagnosis**

## **Imaging**

HCC lesions are characterized by arterial hypervascularity and "wash out" on portal venous phases, since they derive most of their blood supply from the hepatic artery. This is unlike the surrounding liver, which receives its blood supply from both the portal vein and hepatic artery.<sup>31</sup> Diagnostic HCC imaging involves the use of multiphasic liver protocol CT with multiphasic (eg, precontrast, arterial phase, portal venous phase, delayed) intravenous contrast-enhanced MRI.<sup>3,18</sup> The classic imaging profile associated with an HCC lesion is characterized by intense arterial uptake or enhancement followed by contrast washout or hypointensity in the delayed

nonperipheral venous phase. 3,30,32-36 LI-RADS also considers enhancing capsule appearance and threshold growth compared with previous imaging as part of diagnosis using CT or MRI imaging.30 The LI-RADS criteria are applicable only to those with cirrhosis, and a biopsy may be necessary in patients without any history of liver disease. Contrast-enhanced MRI for detection of lesions up to 2 cm has acceptable sensitivity (78%) and excellent specificity (92%) when criteria are applied in appropriate clinical context in patients with known liver disease.<sup>37</sup> The results of a prospective study evaluating the accuracy of contrast-enhanced US (CEUS) and dynamic contrast-enhanced MRI for the diagnosis of liver nodules 2 cm or smaller observed on screening US demonstrated that the diagnosis of HCC can be established without biopsy confirmation if both imaging studies are conclusive.<sup>34</sup> Comparing MRI to CEUS, the sensitivity was 61.7% versus 51.7%, the specificity was 96.6% versus 93.1%, the positive predictive value was 97.4% versus 93.9%, and the negative predictive value was 54.9% versus 50.9%.34 However, CEUS is not commonly used in the United States. Other investigators have suggested that a finding of classical arterial enhancement using a single imaging technique is sufficient to diagnose HCC in patients with cirrhosis and

a See Principles of Imaging (HCC-A\*).

<sup>&</sup>lt;sup>q</sup> See NCCN Guidelines for Older Adult Oncology<sup>†</sup>

Fee Child-Pugh Score (HCC-C\*) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia)

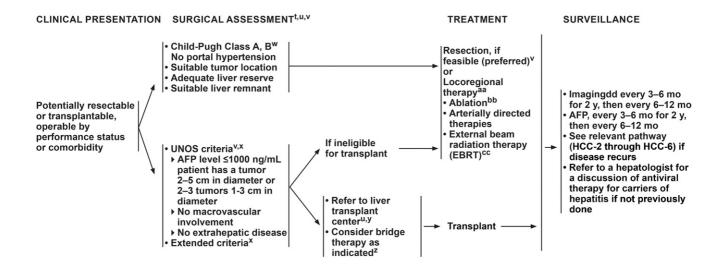
SAn appropriate hepatitis panel should preferably include:

Hepatitis B surface antigen (HBsAg). If the HBsAg is positive, check HBeAg, HBeAb, and quantitative HBV DNA and refer to hepatologist.

<sup>·</sup> Hepatitis B core antibody (HBcAb) IgG. The HBcAb IgM should only be checked in cases of acute viral hepatitis. An isolated HBcAb IgG may still be chronic HBV and should prompt testing for a quantitative HBV DNA

<sup>•</sup> Hepatitis C antibody. If positive, check quantitative HCV RNA and HCV genotype and refer to hepatologist.

<sup>\*</sup>Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.



<sup>t</sup> Discussion of surgical treatment with patient and determination of whether patient is amenable to surgery.

V See Principles of Surgery (HCC-D\*).

W In highly selected Child-Pugh Class B patients with limited resection

y Mazzaferro V, et al. N Engl J Med 1996;334:693-700

cc See Principles of Radiation Therapy (HCC-F\*).

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For relapse, see Initial Workup (HCC-3)

HCC-4

liver nodules between 1 and 2 cm detected during surveillance, thereby reducing the need for a biopsy.<sup>38</sup> In the updated AASLD guidelines, the algorithms for liver nodules between 1 and 2 cm have been changed to reflect these considerations. LI-RADS also offers some guidance regarding the use of CEUS for the diagnosis of HCC.<sup>39</sup>

The NCCN Guidelines' recommendations for diagnostic imaging in the setting of high clinical suspicion for HCC (eg, after identification of a liver nodule on US or in the setting of a rising serum AFP level) apply only to patients with known risk factors for HCC and are adapted from the AASLD guidelines.3 For these patients and patients with an incidental liver mass or nodule found on US or on another imaging exam, the guidelines recommend evaluation using multiphasic abdominal contrastenhanced CT or MRI to determine the enhancement characteristics, extent and number of lesions, vascular anatomy, and extrahepatic disease. Gadolinium contrast is preferred for MRI, because hepatobiliary agents such as gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid that require more subspecialized experience to interpret hepatobiliary phase imaging are not currently included in AASLD or LI-RADS interpretation. The quality of MRI is dependent on patient compliance, since some

patients may be unable to hold their breath. If no mass is detected using multiphasic contrast-enhanced imaging, or if the observed lesion is definitely benign, then the patients should return to a screening program (ie, US and AFP in 6 months). If there is suspicion that the diagnostic imaging test yielded a false negative, then a different imaging method with or without AFP may be considered. If the observation is inconclusive (ie, not definitely HCC but not definitely benign), then multidisciplinary discussion and individualized workup may be pursued, including additional imaging or biopsy. Multidisciplinary team management has been associated with improved outcomes in HCC, including higher rates of treatment, higher rates of curative treatments in early stages, and prolonged survival in advanced disease.40-43

## Serum Biomarkers

Although serum AFP has long been used as a marker for HCC, it is not a sensitive or specific diagnostic test for HCC. Serum AFP levels >400 ng/mL are observed only in a small percentage of patients with HCC. In a series of 1,158 patients with HCC, only 18% of patients had values >400 ng/mL and 46% of patients had normal serum AFP levels <20 ng/mL.<sup>44</sup> In patients with chronic liver disease,

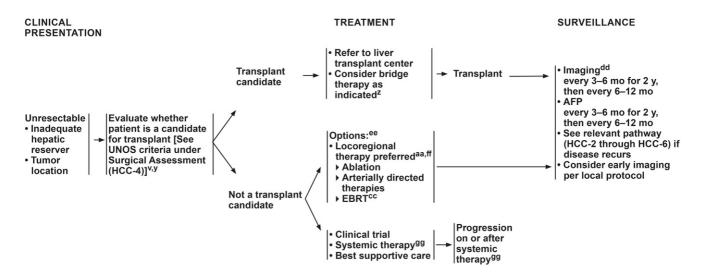
<sup>&</sup>lt;sup>u</sup> Patients with Child-Pugh Class A liver function, who fit UNOS criteria (www.unos.org) and are resectable could be considered for resection or transplant. There is controversy over which initial strategy is preferable to treat such patients. These patients should be evaluated by a multidisciplinary team.

<sup>\*</sup> Extended criteria/downstaging protocols are available through UNOS. See https://optn.transplant.hrsa.gov/media/1200/optn\_policies.pdf#nameddest=Policy\_09.

Z Many transplant centers consider bridge therapy for transplant candidates (See Discussion).
aa See Principles of Locoregional Therapy (HCC-E\*).

bb In well-selected patients with small, properly located tumors ablation should be considered as definitive treatment in the context of a multidisciplinary review.

dd Multiphasic abdominal MRI or multiphase CT scans for liver assessment, CT chest and CT/MRI pelvis. See Principles of Imaging (HCC-A\*).



<sup>\*</sup>Available online, in these guidelines, at NCCN.org.

V See Principles of Surgery (HCC-D\*).

99 See Principles of Systemic Therapy (HCC-G).

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HCC-5

an elevated AFP could be more indicative of HCC than in non-infected patients. <sup>45</sup> Furthermore, AFP can also be elevated in pregnancy and in other cancers such as intrahepatic cholangiocarcinoma, some metastases from colon cancer, lymphoma, and germ cell tumors. <sup>46,47</sup> AFP testing can be useful in conjunction with other test results to guide the management of patients for whom a diagnosis of HCC is suspected. An elevated AFP level in conjunction with imaging results showing the presence of a growing liver mass has been shown to have a high positive predictive value for HCC in 2 retrospective analyses involving small numbers of patients. <sup>48,49</sup> However, the diagnostic accuracy of an absolute AFP cutoff value has not been validated in this setting, and such values may vary by institution and patient population.

Since the level of serum AFP may be elevated in those with certain nonmalignant conditions such as chronic HBV<sup>50</sup> and HCV or be within normal limits in up to 30% patients with HCC<sup>51</sup>, the panel considers an imaging finding of classic enhancement to be more definitive in the diagnostic setting compared with AFP level alone. Additional imaging studies (CT or MRI) are recommended for patients with a rising serum AFP level in the absence of a liver mass. If no liver mass is detected following measurement

of an elevated AFP level, the patient should be followed with AFP testing and liver imaging. Further, assessment of AFP levels may be helpful in monitoring treatment response as appropriate (see "Surveillance," page 557).

The GALAD model, which accounts for gender, age, lens culinaris agglutinin reactive AFP (AFP-L3), AFP, and des-carboxy-prothrombin, is a serum biomarker model used to assess the risk of HCC in patients with chronic liver disease. <sup>52</sup> In validation studies, the GALAD model identified HCC cases in patients with chronic liver disease or nonalcoholic steatohepatitis with a high degree of accuracy. <sup>53–55</sup> The GALADUS score, which combines the GALAD score and US, was found to improve the performance of the GALAD score. <sup>54</sup>

## **Biopsy**

A diagnosis of HCC can often be made noninvasively by imaging in patients with established risk factors for HCC with diagnostic imaging findings on multiphase imaging as described previously. However, there are a few clinical scenarios in which biopsy of a suspected HCC may be considered. First, biopsy may be considered when a lesion is suspicious for malignancy, but multiphasic CT or MRI results do not meet imaging criteria for HCC.<sup>3,19,25,35,56</sup>

Fee Child-Pugh Score (HCC-C\*) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).

y Mazzaferro V, et al. N Engl J Med 1996;334:693-700.

<sup>&</sup>lt;sup>z</sup> Many transplant centers consider bridge therapy for transplant candidates (See Discussion).

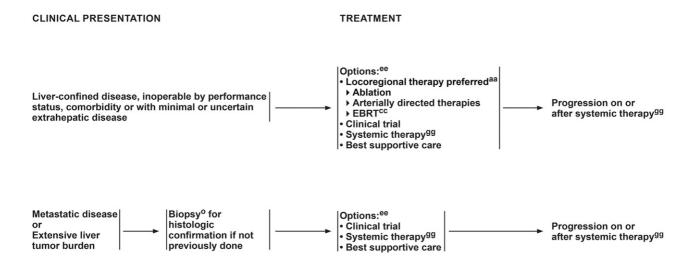
aa See Principles of Locoregional Therapy (HCC-E\*).

cc See Principles of Radiation Therapy (HCC-F\*).

dd Multiphasic abdominal MRI or multiphase CT scans for liver assessment, CT chest and CT/MRI pelvis. See Principles of Imaging (HCC-A\*).

ee Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.

ff Use of chemoembolization has also been supported by randomized controlled trials in selected populations over best supportive care.



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HCC-6

AASLD describes the limitations of biopsy in this scenario, specifically the cost, emotional distress for the patient, risk of complications, and potential sampling error for small lesions. 18 Second, biopsy may be done in patients who are not considered high risk for developing HCC (ie, patients who do not have cirrhosis, chronic HBV, or a previous history of HCC). Third, biopsy may be indicated in patients with conditions associated with formation of nonmalignant nodules that may be confused with HCC during imaging. These conditions include cardiac cirrhosis, congenital hepatic fibrosis, or cirrhosis due to a vascular disorder such as Budd-Chiari syndrome, hereditary hemorrhagic telangiectasia, or nodular regenerative hyperplasia.<sup>57</sup> Finally, biopsy may be considered in patients with elevated CA 19-9 or carcinoembryonic antigen, to rule out intrahepatic cholangiocarcinoma or mixed HCC-cholangiocarcinoma<sup>58,59</sup> or in patients with history of another primary malignancy at risk for metastatic disease. If transplant or resection is a consideration, patients should be referred to a transplant center and/or hepatic surgeon before biopsy since biopsy may not be necessary in certain patients with resectable malignant-appearing masses.

Patients with a nondiagnostic biopsy result should be followed closely, and subsequent additional imaging and/

or biopsy is recommended if a change in nodule size is observed. The guidelines emphasize that a growing mass with a negative biopsy does not rule out HCC. Continual monitoring with a multidisciplinary review including surgeons is recommended because definitive resection may be considered.

## **Initial Workup**

The foundation of an initial workup for patients with suspected HCC is a multidisciplinary evaluation including investigations of the etiologic origin of liver disease, a hepatitis panel for detection of hepatitis B and/or C viral infection (ie, HBsAg, hepatitis B surface antibody, hepatitis B core antibody [HBcAb], HBcAb IgM [recommended only in patients with acute viral hepatitis], and HCV antibodies), an assessment of the presence of comorbidity; imaging studies to detect the presence of metastatic disease, and an evaluation of hepatic function, including a determination of whether portal hypertension is present. The guidelines recommend confirmation of viral load in patients who test positive for HBsAg, HBcAb IgG (since an isolated HBcAb IgG may still indicate chronic HBV infection), and HCV antibodies. If viral load is positive, patients should be evaluated by a hepatologist for consideration of antiviral therapy.<sup>60,61</sup>

O See Principles of Biopsy (HCC-B\*)

aa See Principles of Locoregional Therapy (HCC-E\*)

<sup>&</sup>lt;sup>cc</sup> See Principles of Radiation Therapy (HCC-F\*

ee Order does not indicate preference. The choice of treatment modality may depend on extent/location of disease, hepatic reserve, and institutional capabilities.

<sup>99</sup> See Principles of Systemic Therapy (HCC-G).

<sup>\*</sup>Available online, in these guidelines, at NCCN.org

## First-Line Systemic Therapy

#### **Preferred Regimens**

• Atezolizumab + bevacizumab (Child-Pugh Class A only) (category 1)<sup>a,b,c,1</sup>

## 

- Sorafenib (Child-Pugh Class A [category 1] or B7)d,e,2,3
- Lenvatinib (Child-Pugh Class A only)4,5 (category 1)

- Nivolumab<sup>b,6</sup> (if ineligible for tyrosine kinase inhibitors [TKIs] or other anti-angiogenic agents) (Child-Pugh Class A or B) (category 2B)
- FOLFOX (category 2B)f

## Subsequent-Line Therapy<sup>9</sup> if Disease Progression<sup>h</sup>

- Regorafenib (Child-Pugh Class A only) (category 1)<sup>i,7</sup>
- Cabozantinib (Child-Pugh Class A only) (category 1)<sup>i,8</sup>
   Ramucirumab (AFP ≥400 ng/mL only) (category 1)<sup>i,9</sup>
- · Lenvatinib (Child-Pugh Class A only)
- Sorafenib (Child-Pugh Class A or B7)d,e

## Other Recommended Regimens

Nivolumah

(category 2B)

- (Child-Pugh Class A or B)b,j,10-12
- Nivolumab + ipilimumab (Child-Pugh Class A only)b,i,13
- Pembrolizumah (Child-Pugh Class A only)b,j,k,14
- <sup>a</sup> An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
   <sup>b</sup> See NCCN Guidelines for Management of Immunotherapy-Related Toxicities<sup>†</sup>
- c Patients on atezolizumab + bevacizumab should have adequate endoscopic evaluation and management for esophageal varices within approximately 6 months prior to treatment or according to institutional practice and based on the assessment of bleeding risk
- d See Child-Pugh Score (HCC-C\*) and assessment of portal hypertension (eg, varices, splenomegaly, thrombocytopenia).
   e Caution: There are limited safety data available for Child-Pugh Class B or C patients and dosing is uncertain. Use with extreme caution in patients with elevated bilirubin levels. (Miller AA, et al. J Clin Oncol 2009;27:1800-1805). The impact of sorafenib on patients potentially eligible for transplant is unknown
- f There are limited data supporting the use of FOLFOX, and use of chemotherapy in the context of a clinical trial is preferred. (Qin S, et al. J Clin Oncol 2013;31:3501-
- 9 Larofrectinib and entrectinib are treatment options for patients with hepatocellular carcinoma that is NTRK gene fusion positive. (Drilon A, et al. N Engl J Med 2018;378:731-739; Doebele RC, et al. Lancet Oncol 2020;21:271-282.)
- h There are no data to define optimal treatment for those who progress after first-line systemic therapy, other than sorafenib or nivolumab.
- The data reflect use on or after sorafenib in patients who previously tolerated sorafenib at a dose of at least 400 mg per day.

  Jean to be a previously treated with a checkpoint inhibitor because there is a lack of data for subsequent use of immunotherapy in patients who have previously been treated with a checkpoint inhibitor
- k Consider if MSI-H HCC
- \*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

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Routine chest CT is recommended since lung metastases are typically asymptomatic and a common site of metastases. Bone scan and/or additional bone imaging may be considered as clinically indicated, if suspicious bone pain is present or cross-sectional imaging raises the possibility of bone metastases.<sup>62</sup> Multiphasic contrast-enhanced CT or MRI of the abdomen, CT of the chest, and CT/MRI of the pelvis is also used in the evaluation of the HCC tumor burden to detect the presence of metastatic disease, nodal disease, and vascular invasion; to assess whether evidence of portal hypertension is present; to provide an estimate of the size and location of HCC and the extent of chronic liver disease; and, in the case of patients being considered for resection, to provide an estimate of the future liver remnant (FLR).<sup>33</sup> Enlarged lymph nodes are commonly seen in patients with viral hepatitis, primary biliary cirrhosis, and other underlying liver disorders that predispose patients to HCC.63 Detection of nodal disease by cross-sectional imaging is nonspecific and can be challenging in patients with hepatitis.

#### Assessment of Liver Function

An initial assessment of hepatic function involves liver function testing including measurement of serum levels of bilirubin, aspartate aminotransferase, alanine transaminase,

alkaline phosphatase, measurement of prothrombin time expressed as international normalized ratio, albumin, and platelet count (surrogate for portal hypertension). Other recommended tests include complete blood count, blood urea nitrogen, and creatinine to assess kidney function; creatinine is also an established prognostic marker in patients with liver disease.<sup>64</sup> Further assessment of hepatic functional reserve before hepatic resection in patients with cirrhosis may be performed with different tools such as US and MRI elastography (which may provide and quantify the degree of cirrhosis-related fibrosis), non-focal liver biopsy, and transjugular liver biopsy with pressure measurements.

The Child-Pugh classification has been traditionally used for the assessment of hepatic functional reserve in patients with cirrhosis. 65,66 The Child-Pugh score incorporates laboratory measurements (ie, serum albumin, bilirubin, prothrombin time) as well as more subjective clinical assessments of encephalopathy and ascites. It provides a general estimate of the liver function by classifying patients as having compensated (class A) or decompensated (classes B and C) cirrhosis. Advantages of the Child-Pugh score include ease of performance (ie, can be done at the bedside) and the inclusion of clinical parameters.

The albumin-bilirubin grade model, which considers serum albumin and bilirubin levels, is another helpful tool to assess liver dysfunction.<sup>67,68</sup> It has been shown to be especially helpful in predicting the survival outcome of patients with stable decompensated cirrhosis.<sup>69,70</sup>

An important additional assessment of liver function not included in the Child-Pugh score is an evaluation of signs of clinically significant portal hypertension (ie, esophagogastric varices, splenomegaly, splenorenal shunts and recanalization of the umbilical vein, thrombocytopenia). Evidence of portal hypertension may be evident on CT/MRI.<sup>33,65,66,71,72</sup> Esophageal varices may be evaluated using esophagogastroduodenoscopy or contrast-enhanced cross-sectional imaging.

Model for End-Stage Liver Disease (MELD) is another system for the evaluation of hepatic reserve. MELD is a numerical scale ranging from 6 (less ill) to 40 (gravely ill) for individuals 12 years or older. It is derived using 3 laboratory values (serum bilirubin, creatinine, and international normalized ratio) and was originally devised to provide an assessment of mortality for patients undergoing transjugular intrahepatic portosystemic shunts.73,74 The MELD score has since been adopted by the United Network for Organ Sharing (UNOS; www.unos.org) to stratify patients on the liver transplantation waiting list according to their risk of death within 3 months.<sup>75</sup> The MELD score has sometimes been used in place of the Child-Pugh score to assess prognosis in patients with cirrhosis. Advantages of the MELD score include the inclusion of a measurement of renal function and an objective scoring system based on widely available laboratory tests, although clinical assessments of ascites and encephalopathy are not included. It is currently unclear whether the MELD score is superior to the Child-Pugh score as a predictor of survival in patients with liver cirrhosis. The MELD score has not been validated as a predictor of survival in patients with cirrhosis who are not on a liver transplantation waiting list.<sup>76</sup> Although the MELD model is used to stratify organ access for transplantation, it also favors patients with renal dysfunction. Serum creatinine, an important component of the MELD score, can be an unreliable marker of renal dysfunction, especially in patients with cirrhosis.77

## **Staging**

Clinical staging systems for the patient with cancer can provide a more accurate prognostic assessment before and after a particular treatment intervention, and they may be used to guide treatment decision-making including enrollment in clinical trials. Therefore, staging can have a critical impact on treatment outcome by facilitating appropriate patient selection for specific therapeutic interventions and by providing risk stratification information after treatment. The key factors affecting prognosis in

patients with HCC are the clinical stage, growth rate of the tumor, the general health of the patient, the liver function of the patient, and the treatments administered. Many staging systems for patients with HCC have been devised. Each of the staging systems includes variables that evaluate one or more of the factors listed previously. For example, the Child-Pugh<sup>81</sup> and MELD scores<sup>73</sup> can be considered to be staging systems that evaluate aspects of liver function.

Due to the unique characteristics of HCC that vary with geographic region, many of the existing staging systems are specific to the region in which they are developed and there is no universally accepted staging system that could be used across all institutions in different countries. The Barcelona Clinic Liver Cancer and the Hong Kong Liver Cancer staging systems are among the most widely used. Although no particular staging system (with the exception of the Child-Pugh score and TNM staging system) is currently used in these guidelines, following an initial workup, patients are stratified into one of the following 4 categories:

- Potentially resectable or transplantable, operable by performance status or comorbidity
- Unresectable disease
- Liver-confined disease, inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic disease
- Metastatic disease

## **Treatment Options**

All patients with HCC should be carefully evaluated by an experienced multidisciplinary team for the many availabel treatment options. It is important to reiterate that the management of patients with HCC is complicated by the presence of underlying liver disease. Furthermore, different etiologies of HCC and their effects on the host liver may impact treatment response and outcome. These complexities make treatment decisions in patients with HCC challenging and are the reason for multidisciplinary care. Given the comorbidities associated with this disease, patients need careful consideration of treatment choice given the risk of potential toxicities from treatment and potential benefits.

## Surgery

Partial hepatectomy is a potentially curative therapy for patients with a solitary tumor of any size with no evidence of gross vascular invasion. Partial hepatectomy for well-selected patients with HCC can now be performed with low operative morbidity and mortality ( $\leq$ 5%). Results of large retrospective studies have shown 5-year survival rates of >50% for patients undergoing liver resection for HCC, AL-86 and some studies suggest that for selected

patients with preserved liver function and early-stage HCC, liver resection is associated with a 5-year survival rate of approximately 70%. <sup>86–88</sup> However, recurrence rates at 5 years following liver resection have been reported to exceed 70%. <sup>85,89</sup>

Since liver resection for patients with HCC includes removal of functional liver parenchyma in the setting of underlying liver disease, careful patient selection, based on patient characteristics as well as characteristics of the liver and the tumor(s), is essential. Assessments of patient performance status must be considered; the presence of comorbidity has been shown to be an independent predictor of perioperative mortality.90 Likewise, estimates of overall liver function and the size and function of the putative FLR, as well as technical considerations related to tumor and liver anatomy, must be considered before a patient is determined to have potentially resectable disease. Univariate analyses from a database study including 141 patients with HCC and liver cirrhosis who underwent resection at a German hospital showed that patient age greater than 70 years (P<.05), Clavien grade of complications (P<.001), positive lymph vessels (P<.001), mechanical ventilation (P<.001), and body mass index (P<.05) were significantly associated with survival.<sup>91</sup>

Resection is recommended only in the setting of preserved liver function. The Child-Pugh score provides an estimate of liver function, although it has been suggested that it is more useful as a tool to rule out patients for liver resection (ie, serving as a means to identify patients with substantially decompensated liver disease).92 An evaluation of the presence of significant portal hypertension is also an important part of the surgical assessment. A metaanalysis including 11 studies showed that clinically significant portal hypertension is associated with increased 3and 5-year mortality (pooled odds ratio [OR], 2.09; 95% CI, 1.52-2.88 for 3-year mortality; pooled OR, 2.07; 95% CI, 1.51-2.84 for 5-year mortality), as well as postoperative clinical decompensation (pooled OR, 3.04; 95% CI, 2.02–4.59).93 In general, evidence of optimal liver function in the setting of liver resection is characterized by a Child-Pugh class A score and absence of portal hypertension. However, in highly selected cases, patients with a Child-Pugh class B score may be considered for limited liver resection, particularly if liver function tests are normal and clinical signs of portal hypertension are absent. Further, limited resection may be feasible in cases where portal hypertension is mild. A prospective observational study of 223 cirrhotic patients with HCC showed that, though portal hypertension was significantly associated with liver-related morbidity following resection, it was only associated with worse survival when there was biochemical evidence of liver decompensation. A multivariate analysis showed that albumin, but not portal hypertension, was significantly associated with survival after resection. 94

With respect to tumor characteristics and estimates of the FLR following resection, preoperative imaging is essential for surgical planning.<sup>33</sup> CT/MRI can be used to facilitate characterization of the number and size of the HCC lesions to detect the presence of satellite nodules, extrahepatic metastasis, and tumor invasion of the portal vein or the hepatic veins/inferior vena cava, and to help establish the location of the tumors with respect to vascular and biliary structures.

Optimal tumor characteristics for liver resection are solitary tumors without major vascular invasion. Although no limitation on the size of the tumor is specified for liver resection, the risk of vascular invasion and dissemination increases with size. B3,95 However, in one study no evidence of vascular invasion was seen in approximately one-third of patients with single HCC tumors  $\geq\!10$  cm. We have the less, the presence of macro- or microscopic vascular invasion is a strong predictor of HCC recurrence. A3,96,97 The role of liver resection for patients with limited and resectable multifocal disease and/or signs of major vascular invasion is controversial, as the recurrence rates are extremely high. B2,96,98

Another critical preoperative assessment includes evaluation of the postoperative FLR volume, which serves as an indicator of postoperative liver function. Cross-sectional imaging is used to measure the FLR and total liver volume. The ratio of future remnant/total liver volume (subtracting tumor volume) is then determined.<sup>99</sup> The panel recommends that this ratio be at least 20% in patients without cirrhosis and at least 30%-40% in patients with chronic liver disease and a Child-Pugh A score. 100,101 For patients with an estimated FLR/total liver volume ratio below recommended values who are otherwise suitable candidates for liver resection, preoperative portal vein embolization (PVE) should be considered. PVE is a safe and effective procedure for redirecting blood flow toward the portion of the liver that will remain following surgery.102 Hypertrophy is induced in these segments of the liver while the embolized portion of the liver undergoes atrophy. 103 There are some investigational methods focused on improving FLR growth, such as PVE combined with hepatic vein embolization or with arterial embolization The estimated FLR function, which accounts for individual differences in body surface area, can also be calculated. 104 A comparison of the 2 methods showed that the estimated FLR function deviated from the FLR by ≥5% in 32% of 116 patients enrolled. 105

## **Liver Transplantation**

Liver transplantation is a potentially curative therapeutic option for patients with early HCC. It is especially appealing since it removes both detectable and undetectable tumor lesions, treats underlying liver cirrhosis, and avoids surgical complications associated with a small FLR. However, there is also a risk of potential complications such as

early mortality and issues related to chronic immunosuppression. 106 In a landmark study published in 1996, Mazzaferro et al proposed the Milan criteria (single tumors <5 cm in diameter or no more than 3 nodules <3 cm in diameter in patients with multiple tumors and no macrovascular invasion) for patients with unresectable HCC and cirrhosis. 107 The 4-year OS and recurrence-free survival (RFS) rates were 85% and 92%, respectively, when liver transplantation was restricted to a subgroup of patients meeting the Milan selection criteria. These results have been supported by studies in which patient selection for liver transplantation was based on these criteria. 108 These selection criteria were adopted by UNOS because they identify a subgroup of patients with HCC whose liver transplantation results are similar to those who underwent liver transplantation for end-stage cirrhosis without HCC.

The UNOS criteria (AFP level ≤1,000 ng/mL and radiologic evidence of either a single lesion >2 cm and <5 cm in diameter, or 2-3 lesions >1 cm and <3 cm in diameter, and no evidence of macrovascular involvement or extrahepatic disease) specify that patients eligible for liver transplantation should not be candidates for liver resection.<sup>109</sup> Expansion of the Milan/UNOS criteria to provide patients who have marginally larger HCC tumors with liver transplant eligibility is an active area of debate, with exceptional cases frequently prompting analysis and revisions.89,108,110,111 An expanded set of criteria including patients with a single HCC tumor < 6.5 cm, with a maximum of 3 total tumors with no tumor larger than 4.5 cm (and cumulative tumor size <8 cm) as liver transplant candidates has been proposed by Yao et al at the University of California at San Francisco. 112,113

Resection or liver transplantation can be considered for patients with Child-Pugh class A liver function who meet UNOS criteria (www.unos.org/) and are resectable. Controversy exists over which initial strategy is preferable to treat such patients. The guidelines recommend that these patients be evaluated by a multidisciplinary team when deciding an optimal treatment approach. The Organ Procurement and Transplantation Network (OPTN) has proposed imaging criteria for patients with HCC who may be candidates for transplant. 56 Specifically, they propose a classification system for nodules identified by well-defined imaging from contrast-enhanced CT or MRI. OPTN also provides guidance on equipment specifications and use of a standardized protocol. Although the panel does not have a recommendation regarding liver transplantation in older adults with HCC, some centers report transplant in highly selected patients older than 70 years. 114-117

## Bridge Therapy

Bridge therapy is used to decrease tumor progression and the dropout rate from the liver transplantation waiting list.<sup>118</sup> It is considered for patients who meet the transplant criteria. An analysis including 205 patients from a transplant center registry who had HCC showed that bridging locoregional therapy was associated with survival after transplant (P=.005).<sup>119</sup> A number of studies have investigated the role of locoregional therapies as a bridge to liver transplantation in patients on a waiting list.<sup>120,121</sup> These studies included radiofrequency ablation (RFA)/microwave ablation (MWA);<sup>122–125</sup> transarterial embolization (TAE);<sup>126,127</sup> transarterial chemoembolization (TACE),<sup>124,128</sup> including conventional TACE,<sup>124,129,130</sup> and TACE with drug-eluting beads (DEB-TACE);<sup>131</sup> selective internal radiotherapy or radioembolization (TARE) with yttrium-90 (Y-90) microspheres;<sup>132</sup> external beam radiation therapy (EBRT);<sup>133</sup> and TACE followed by EBRT,<sup>134</sup> as "bridge" therapies.

## **Downstaging Therapy**

Downstaging therapy is used to reduce the tumor burden in selected patients with more advanced HCC (without distant metastasis) who are beyond the accepted transplant criteria with the goal of future transplant. 118,135,136 A meta-analysis including 3 studies showed that downstaging therapy was associated with increased 1-year survival (RR, 1.11; 95% CI, 1.01–1.23) and 5-year survival (RR, 1.17; 95% CI, 1.03-1.32) after transplant, compared with transplant alone.<sup>137</sup> Downstaging therapy did not significantly increase RFS. However, the 3 studies included in these analyses were heterogeneous and biased by the fact that outcomes were measured in patients who responded well to therapy. A systematic review including 13 studies with 950 patients showed that downstaging decreased tumor burden to within Milan criteria (pooled success rate of 0.48; 95% CI, 0.39-0.58), with recurrence rates after transplantation at 16% (95% CI, 0.11-0.23). 138 Candidates are eligible for a standardized MELD exception if, before completing locoregional therapy, they have lesions that meet one of the following: (1) one lesion >5 cm and  $\leq$ 8 cm; (2) 2 or 3 lesions that meet all of the following: each lesion ≤5 cm, with at least 1 lesion >3 cm and a total diameter of all lesions ≤8 cm; and 3) 4 or 5 lesions each <3 cm, and a total diameter of all lesions ≤8 cm. <sup>139</sup> The University of California at San Francisco criteria can be used as the current limit for consideration of downstaging, and potential candidates for this therapy should be assessed by a transplant center.

The NCCN Guidelines recommend that patients meeting the UNOS criteria be considered for transplantation using either cadaveric or living donation. Patients with tumor characteristics that are marginally outside of the UNOS guidelines may be considered for transplantation at select institutions. For patients with initial tumor characteristics beyond the Milan criteria who have undergone successful downstaging therapy (ie, tumor currently meeting Milan criteria), transplantation can also be considered.

## **Locoregional Therapies**

#### Ablation

In an ablative procedure, tumor necrosis can be induced either by thermal ablation (RFA or MWA), chemical ablation (percutaneous ethanol injection [PEI] or acetic acid injection), or cryoablation. Ablative procedures can be performed by percutaneous, laparoscopic, or open approaches. RFA and MWA have largely replaced PEI, although PEI is used in select patients.

The safety and efficacy of RFA and PEI in the treatment of Child-Pugh class A patients with early-stage HCC tumors (either a single tumor  $\leq 5$  cm or multiple tumors [up to 3 tumors] each  $\leq 3$  cm) has been compared in a number of RCTs. <sup>140–147</sup> Both RFA and PEI were associated with relatively low complication rates. RFA was shown to be superior to PEI with respect to complete response rate (65.7% vs 36.2%, respectively; P=.0005) <sup>145</sup> and local recurrence rate (3-year local recurrence rates were 14% and 34%, respectively; P=.012). <sup>143</sup> Local tumor progression rates were also significantly lower for RFA than for PEI (4-year local tumor progression rates were 1.7% and 11%, respectively; P=.003). <sup>144</sup>

RFA and PEI have also been compared with resection in randomized studies. In the only randomized study that compared PEI with resection in 76 patients without cirrhosis, with 1 or 2 tumors 3 cm or smaller, PEI was equally as effective as resection.<sup>148</sup> Conversely, studies that have compared RFA and resection have failed to provide conclusive evidence (reviewed by Weis et al<sup>147</sup>). RFA and liver resection in the treatment of patients with HCC have been compared in randomized prospective studies. 149-153 The results of one randomized trial showed a significant survival benefit for resection over RFA in 235 patients with small HCC conforming to the Milan criteria. 150 The 5-year OS rates were 54.8% and 75.6%, respectively, for the RFA group and resection. The corresponding RFS rates for the 2 groups were 28.7% and 51.3%, respectively. However, more patients in the resection group were lost to followup than the RFA group. Conversely, other randomized studies demonstrated that percutaneous local ablative therapy with RFA is as effective as resection for patients with early-stage disease (eg, small tumors). 149,151-153 These studies failed to show statistically significant differences in OS and DFS between the 2 treatment groups. In addition, in one of the studies, tumor location was an independent risk factor associated with survival. 151 These studies, however, were limited by the small number of patients (180 and 168 patients, respectively) and the lack of a noninferiority design. Nevertheless, results from these studies support ablation as an alternative to resection in patients with small (<3 cm), properly located tumors.

RFA has been compared with resection in some metaanalyses, which have shown that resection is generally associated with better survival outcomes than RFA $^{154-156}$  but is associated with more complications and morbidity from complications. $^{154,156}$  Subgroup analyses from one meta-analysis showed no significant differences in 1-year mortality and disease recurrence when including only studies with patients who had solitary or small tumors (>3 cm). $^{155}$  One meta-analysis comparing RFA to resection in recurrent HCC (including 6 retrospective comparative studies) showed that 3- and 5-year DFS rates were greater for resection, relative to RFA (OR, 2.25; 95% CI, 1.37–3.68; P=.001; OR, 3.70; 95% CI, 1.98–6.93; P<.001, respectively). $^{157}$ 

MWA is an alternative to RFA for the treatment of patients with small or unresectable HCC.<sup>158–162</sup> So far, only 2 randomized trials have compared MWA with resection and RFA.<sup>158,162</sup> In the RCT that compared RFA with percutaneous microwave coagulation, no significant differences were observed between these 2 procedures in terms of therapeutic effects, complication rates, and the rates of residual foci of untreated disease.<sup>158</sup> In a randomized study that evaluated the efficacy of MWA and resection in the treatment of HCC conforming to Milan criteria, MWA was associated with lower DFS rates than resection with no differences in OS rates.<sup>162</sup>

Irreversible electroporation (IRE) is an emerging modality for tumor ablation.<sup>163</sup> It targets tumor tissue by delivering nonthermal high-voltage electric pulses. By doing so, it increases permeability of the cell membrane, disrupting cellular homeostasis and triggering apoptosis. IRE has some advantages over RFA, notably the lack of "heat sink" effect and the ability to treat near vessels, bile ducts, and other critical structures. 164,165 However, IRE can cause cardiac arrhythmias and uncontrolled muscle contractions.166 Some small studies have shown that IRE treatment of unresectable HCC is safe and feasible. 167-169 In a small nonrandomized trial including 30 patients with malignant liver tumors, none of the 8 patients with HCC experienced a recurrence through 6-month follow-up. 169 Recurrences have been reported after IRE for larger tumors. 166,168 Larger studies are needed to determine the effectiveness of IRE for local HCC treatment.

Although inconclusive, availabel evidence suggests that the choice of ablative therapy for patients with early-stage HCC should be based on tumor size and location, underlying liver function, and availabel local radiologist expertise and experience. Ablative therapies are most effective for tumors <3 cm that are in an appropriate location away from other organs and major vessels/bile ducts, with the best outcomes in tumors <2 cm.

## **Arterially Directed Therapies**

Arterially directed therapies that are currently in use include TAE, conventional TACE, DEB-TACE, and selective internal radiotherapy/TARE with Y-90 microspheres. The

principle of TAE is to reduce or eliminate blood flow to the tumor, resulting in tumor ischemia followed by tumor necrosis. Gelatin sponge particles, polyvinyl alcohol particles, and polyacrylamide microspheres have been used to block arterial flow. TAE has been shown to be an effective treatment option for patients with unresectable HCC.  $^{170-173}$  In a multicenter retrospective study of 476 patients with unresectable HCC, TAE was associated with prolonged survival compared with supportive care (P=.0002). $^{171}$  In a multivariate analysis, tumor size <5 cm and earlier CLIP (Cancer of the Liver Italian Program) stage were independent factors associated with a better survival.

TACE is distinguished from TAE in that, in addition to arterial blockade, the goal is to also deliver a highly concentrated dose of chemotherapy to tumor cells, prolong the contact time between the chemotherapeutic agents and the cancer cells, and minimize systemic toxicity of chemotherapy.<sup>174</sup> The results of 2 RCTs and one retrospective case-control study have shown a survival benefit for TACE compared with supportive care in patients with unresectable HCC.<sup>175–177</sup> In a randomized trial, the effectiveness of TAE was compared with that of doxorubicin-based TACE in 101 patients with HCC.<sup>178</sup> Study investigators did not find statistically significant differences in response, progression free survival (PFS), and OS between the 2 groups. Some institutions prefer the use of bland embolization using particles without chemotherapy.<sup>178</sup>

DEB-TACE has also been evaluated in patients with unresectable HCC. 179-186 A randomized study (PRECISION V) of 212 patients with localized, unresectable HCC with Child-Pugh class A or B cirrhosis and without nodal involvement, showed no difference in CR, objective response, and disease control between DEB TACE with doxorubicin-eluting embolic beads and conventional TACE with doxorubicin.<sup>181</sup> Overall, DEB-TACE was not superior to conventional TACE with doxorubicin (P=.11) in this study. In a subgroup analysis, DEB-TACE was associated with a significant increase in objective response (P=.038) compared with conventional TACE in patients with Child-Pugh class B, ECOG performance status 1, bilobar disease, and recurrent disease. DEB-TACE was also associated with improved tolerability with a significant reduction in serious liver toxicity and a significantly lower rate of doxorubicin-related side effects, compared with conventional TACE.<sup>181</sup> The findings from a meta-analysis of 28 studies suggest that DEB-TACE led to longer OS compared with TARE and conventional TACE. 187 However, there were lower complications associated with TARE.

TARE is a method that involves internal delivery of high-dose beta radiation to the tumor-associated capillary bed, thereby sparing the normal liver tissue. TARE is accomplished through the catheter-based administration of microspheres (glass or resin microspheres) embedded with Y-90, an emitter of beta radiation. There is a growing

body of literature to suggest that radioembolization might be an effective treatment option for patients with liverlimited, unresectable disease, 190-195 though additional RCTs are needed to determine the relative risks and benefits of TARE with Y-90 microspheres in patients with unresectable HCC and long-term impact on liver function. 196 Delivery of 205 Gy or greater to the tumor may be associated with increased OS. 197 Although radioembolization with Y-90 microspheres, like TAE and TACE, involves some level of particle-induced vascular occlusion, it has been proposed that such occlusion is more likely to be microvascular than macrovascular, and that the resulting tumor necrosis is more likely to be induced by radiation rather than ischemia.<sup>190</sup> RCTs have shown that Y-90 is not superior to sorafenib for treating advanced HCC. 198,199 Radioembolization may be appropriate in some patients with advanced HCC, 198, 199 specifically patients with segmental or lobar portal vein, rather than main portal vein thrombosis. 190

## Radiation Therapy

Radiation therapy options for patients with unresectable or inoperable HCC include EBRT and stereotactic body radiation therapy (SBRT). EBRT allows focal administration of high-dose radiation to liver tumors while sparing surrounding liver tissue, thereby limiting the risk of radiation-induced liver damage in patients with unresectable or inoperable HCC.<sup>200,201</sup> Advances in EBRT, such as intensity-modulated radiation therapy and image-guided radiotherapy, have allowed for enhanced delivery of higher radiation doses to the tumor while sparing surrounding critical tissue. SBRT is an advanced technique of EBRT that delivers large ablative doses of radiation. There is growing evidence (primarily from non-RCTs) supporting the usefulness of SBRT for patients with unresectable, locally advanced, or recurrent HCC.<sup>202–206</sup>

Most tumors, irrespective of their location, may be amenable to SBRT, intensity-modulated radiation therapy, or conformal EBRT. SBRT dosing is usually 30 to 50 Gy in 3 to 5 fractions, depending on the ability to meet normal organ constraints and underlying liver function. 202,203,207-209 Hypofractionated schedules may also be considered.<sup>210</sup> SBRT is often used for patients with 1 to 3 tumors with minimal or uncertain extrahepatic disease. There is no strict size limit, so SBRT may be used for larger lesions if there is sufficient uninvolved liver and liver radiation dose constraints can be respected. Most safety and efficacy data on the use of SBRT are availabel for patients with HCC and Child-Pugh A liver function; limited safety data are availabel for the use of SBRT in patients with Child-Pugh B or poorer liver function. 203,206,207,210,211 Those with Child-Pugh B cirrhosis may require dose modifications and strict dose constraint adherence to increase safety in this population. The safety of SBRT for patients

with Child-Pugh C cirrhosis has not been established, because there are not likely to be clinical trials availabel for this group of patients with a very poor prognosis.

The relative effectiveness of locoregional therapies compared with resection or liver transplantation in the treatment of patients with HCC has not been established. The consensus of the panel is that liver resection or transplan-

NCCN Recommendations for Locoregional Therapies

consensus of the panel is that liver resection or transplantation, if feasible, is preferred for patients who meet surgical or transplant selection criteria because these are established potentially curative therapies. Locoregional therapy (eg, ablation, arterially directed therapies, EBRT/SBRT) is the preferred treatment approach for patients who are not amenable to surgery or liver transplantation.

All tumors considered for ablation should be amenable to complete treatment with a margin of normal tissue around the tumor. Tumors should be in a location accessible for percutaneous, laparoscopic, or open approaches. Lesions abutting key structures such as the bile ducts, stomach, bowel, gallbladder, or diaphragm may be difficult locations for ablation although hydrodissection techniques can be used to safely treat in some instances. The panel emphasizes that caution should be exercised when ablating lesions near these structures to decrease complications. Similarly, ablative treatment of tumors located on the liver capsule may cause tumor rupture with track seeding, especially with direct puncture techniques. Tumor seeding along the needle track has been reported in <1% of patients with HCC treated with RFA.212-214 Lesions with subcapsular location and poor differentiation seem to be at higher risk for this complication.<sup>212</sup> During an ablation procedure, major vessels in close proximity to the tumor can absorb large amounts of heat (known as the "heat sink effect"), which can decrease the effectiveness and significantly increase local recurrence rates.

The consensus of the panel is that ablation alone may be a curative treatment of tumors  $\leq 3$  cm. In well-selected patients with small, properly located tumors, ablation should be considered as definitive treatment in the context of a multidisciplinary review. Tumors between 3 and 5 cm may be treated with a combination of MWA and/or arterially directed therapies to prolong survival, as long as the tumor location is favorable to ablation and underlying liver function is adequate. The panel recommends that patients with unresectable or inoperable lesions  $\geq 5$  cm should be considered for treatment using arterially directed therapies, EBRT, or systemic therapy.

All HCC tumors, irrespective of location in the liver, may be amenable to arterially directed therapies, provided that the arterial blood supply to the tumor can be isolated. An evaluation of the arterial anatomy of the liver, patient's performance status, and liver function is necessary prior to the initiation of arterially directed

therapy. In addition, more individualized patient selection that is specific to the particular arterially directed therapy being considered is necessary to avoid significant treatment-related toxicity. General patient selection criteria for arterially directed therapies include unresectable or inoperable tumors not amenable to ablation therapy only, and the absence of large-volume extrahepatic disease. Minimal extrahepatic disease is considered a "relative" contraindication for arterially directed therapies.

All arterially directed therapies are relatively contraindicated in patients with bilirubin >3 mg/dL unless segmental treatment can be performed. Outside of segmental therapy, TARE with Y-90 microspheres has an increased risk of radiation-induced liver disease in patients with bilirubin >2 mg/dL. 192 Arterially directed therapies are safe to use in patients with limited tumor invasion of the portal vein but are contraindicated in patients with Child-Pugh class C disease, unless the goal of therapy is to bridge the patient to transplant. It is also important to note that the contrast agent used may be nephrotoxic, and, thus, these therapies should not be used if creatinine clearance is elevated.

The panel recommends that EBRT or SBRT be considered as an alternative to ablation and/or embolization techniques when these therapies have failed or are contraindicated (in patients with unresectable disease characterized as extensive or otherwise not suitable for liver transplantation and those with local disease but who are not considered candidates for surgery due to performance status or comorbidity). Radiotherapy should be guided by imaging to improve treatment accuracy and reduce toxicity. Palliative EBRT is appropriate for symptom control and/or prevention of complications from metastatic HCC lesions in bone or brain.<sup>219</sup> The panel encourages prospective clinical trials evaluating the role of SBRT in patients with unresectable, locally advanced, or recurrent HCC.

## Systemic Therapy

## Sorafenib

Sorafenib, an oral multikinase inhibitor that suppresses tumor cell proliferation and angiogenesis, was evaluated in 2 randomized, placebo-controlled, phase III trials for the treatment of patients with advanced or metastatic HCC. <sup>220,221</sup>

In one of these phase III trials (SHARP trial), 602 patients with advanced HCC were randomly assigned to sorafenib or best supportive care. In this study, advanced HCC was defined as patients not eligible for or those who had disease progression after surgical or locoregional therapies. The majority of the patients had preserved liver function (≥95% of patients classified as Child-Pugh class A) and good performance status (>90% of patients had ECOG performance status of 0 or 1). Median OS was

significantly longer in the sorafenib arm (10.7 months in the sorafenib arm vs 7.9 months in the placebo group; hazard ratio [HR], 0.69; 95% CI, 0.55–0.87; P<.001). In the Asia-Pacific study, another phase III trial with a similar design to the SHARP study, 226 patients were randomly assigned to sorafenib or placebo arms (150 and 76 in sorafenib and placebo arms, respectively). While the HR for the sorafenib arm compared with the placebo arm (HR, 0.68; CI, 0.50–0.93; P=.014) was nearly identical to that reported for the SHARP study, the median OS was strikingly lower in both treatment and placebo groups in the Asia-Pacific study (6.5 vs 4.2 months).

## Lenvatinib

Lenvatinib is an inhibitor of vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor, platelet-derived growth factor receptor (PDGFR), and other growth signaling kinases. In the phase III randomized REFLECT trial, patients with unresectable HCC (N=954) were randomized to receive either lenvatinib or sorafenib as first-line treatment. The trial was designed to demonstrate noninferiority or superiority of lenvatinib; the prespecified boundary for noninferiority was met with median OS of 13.6 months in the lenvatinib arm compared with 12.3 months for sorafenib (HR, 0.92; 95% CI, 0.79–1.06). Based on results of the REFLECT trial, the FDA approved lenvatinib in 2018 as first-line treatment of patients with unresectable HCC.

The combination of lenvatinib and pembrolizumab, an anti-PD-1 antibody, was investigated in a phase Ib study with 104 patients with unresectable HCC.<sup>223</sup> Using mRECIST criteria, the objective response rate (ORR) was 46.0% (95% CI, 36.0%–56.3%). The median PFS and OS were 9.3 and 22 months respectively. This combination is under investigation in a randomized phase III trial against lenvatinib alone for the frontline treatment of unresectable or metastatic HCC (ClinicalTrials.gov identifier: NCT03713593).

## Atezolizumab and Bevacizumab

Bevacizumab, a VEGF inhibitor, has modest clinical activity as a single agent or in combination with erlotinib or chemotherapy in phase II studies in patients with advanced HCC. <sup>224–228</sup> A published abstract reported that atezolizumab combined with bevacizumab showed an ORR of 34% in the first-line treatment option of unresectable or metastatic HCC in a phase 1b trial. <sup>229</sup> The IMbrave150 phase III trial enrolled 501 patients with unresectable HCC and Child Pugh A liver function, with randomization to either the combination of atezolizumab and bevacizumab or sorafenib as first-line treatment. All patients were required to have an upper endoscopy within 6 months prior to enrollment due to risk of upper gastrointestinal bleeding observed in prior phase 2 studies of

bevacizumab in HCC.<sup>225,230</sup> The IMbrave150 study showed that the combination of atezolizumab plus bevacizumab significantly improved outcomes compared with sorafenib, with the 12-month OS (67.2% vs 54.6%; HR; 0.58, *P*<.001) and median PFS (6.8 vs 4.3 months; HR, 0.59; P<.001).<sup>231</sup> Analyses from an independent reviewer (using HCC RECIST criteria) comparing the atezolizumab and bevacizumab combination to sorafenib showed an ORR of 27.3% versus 11.9% (5.5% vs 0% CR, 21.8% vs 11.9% partial response), with stable disease in 46.3% versus 43.4% of patients and progressive disease in 19.6% versus 24.5%. Duration of response >6 months was estimated to be 87.6% in the atezolizumab and bevacizumab arm and 59.1% in the sorafenib arm. Updated data from a published abstract revealed a median OS of 19.2 months for patients in the atezolizumab and bevacizumab group versus 13.4 months for patients in the sorafenib group (HR, 0.66; P=.0009).<sup>232</sup> Before the start of the atezolizumab plus bevacizumab regimen, patients should have adequate endoscopic evaluation and management for esophageal varices within approximately 6 months before treatment or according to institutional practice and based on the assessment of bleeding risk.

## Subsequent-Line Therapy if Disease Progression

Until recently, there have been no subsequent-line systemic therapy options for patients with HCC who have disease progression on or after sorafenib. Recent advancements have produced some effective systemic therapy options for these patients. However, it should be noted that it is unclear what the benefits of these systemic therapy options are for patients who receive the atezolizumab and bevacizumab regimen as a first-line treatment option and what subsequent agents to use if the disease progresses. The first drug to get approved for HCC after sorafenib was regorafenib, an oral multi-kinase inhibitor with activity against VEGFR1-3, PDGFRB, KIT, RET, RAF-1, and other growth signaling kinases. The randomized, doubleblind, placebo-controlled, international phase III RESORCE trial assessed the efficacy and safety of regorafenib in 573 patients with HCC and Child-Pugh A liver function who progressed on sorafenib and who tolerated sorafenib at a dose of 400 mg per day for at least 20 of the prior 28 days of treatment.<sup>233</sup> Compared with the placebo, regorafenib improved median OS (10.6 vs 7.8 months, respectively; HR, 0.63; 95% CI, 0.50–0.79; P<.001), median PFS by mRECIST (3.1 vs 1.5 months; HR, 0.46; 95% CI, 0.37–0.56; P<.001), median time to progression (TTP) by mRECIST (3.2 vs 1.5 months; HR, 0.44; 95% CI, 0.36–0.55; P<.001), ORR (11% vs 4%; P=.005), and disease control (65% vs 36%; P<.001). Adverse events were universal among patients randomized to receive regorafenib (n=374), with the most frequent grade 3 or 4 treatment-related events being hypertension (15%), hand-foot skin reaction (13%), fatigue (9%), and

diarrhea (3%). Seven deaths that occurred were considered by the investigators to have been related to treatment with regorafenib. Based on the results of this trial, the FDA approved regorafenib in 2017 for patients with HCC who experienced progression on or after sorafenib.

Cabozantinib, another oral multikinase inhibitor with potent activity against VEGFR1-3 and MET among other targets, was assessed in the phase III randomized CELES-TIAL trial including 707 patients with advanced HCC who have progressed on or after sorafenib, with 7.6% of the sample having received more than one line of previous treatment.<sup>234</sup> Median OS and PFS were significantly greater in patients randomized to receive cabozantinib (10.2 and 5.2 months, respectively), compared with patients randomized to receive a placebo (8.0 and 1.9 months, respectively) (HR, 0.76; 95% CI, 0.63–0.92; P=.005 for OS; HR, 0.44; 95% CI, 0.36–0.52; P < .001 for PFS), as was the ORR (4% vs 0.4%, P=.009). Though the objective response rate was better in the cabozantinib arm than in the placebo arm (P=.009), this value was low, with a PR having been reported in only 4% of patients who received cabozantinib (vs. 0.4% in patients who received a placebo). A subsequent analysis showed that the benefits of cabozantinib spanned across a range of AFP levels.<sup>235</sup> The on-treatment AFP response was higher in the cabozantinib arm, which was linked to longer OS and PFS. Cabozantinib was approved by the FDA in 2019 for patients with Child-Pugh A liver function who have disease progression on or after sorafenib.

In a phase III randomized REACH trial, the monoclonal antibody against VEGFR2, ramucirumab, was assessed as second-line therapy after sorafenib in patients with advanced HCC (n=565).<sup>236,237</sup> Though this regimen did not improve median OS (9.2 vs 7.6 months; HR, 0.87), median PFS (HR, 0.63; 95% CI, 0.52–0.75; P<.001) and TTP (HR, 0.59; 95% CI, 0.49–0.72; P<.001) were improved, relative to the placebo group. <sup>236</sup> A subgroup analysis in patients with a baseline AFP level of ≥400 ng/mL (n=250) showed that the median OS and PFS were 7.8 months (HR, 0.67) and 2.7 months, respectively, for patients in the ramucirumab arm, and 4.2 and 1.5 months, respectively, for patients in the placebo arm. Analyses of patient-focused outcomes showed that deterioration of symptoms was not significantly different in patients randomized to receive ramucirumab, compared with the placebo group.<sup>237</sup>

Based on these findings, the REACH-2 randomized phase III trial assessed the efficacy of ramucirumab in patients with HCC who had disease progression on or after sorafenib who had a baseline AFP level of  $\geq$ 400 ng/mL (n=292).<sup>238</sup> OS and PFS were greater in patients who received ramucirumab with best supportive care, compared with patients randomized to receive a placebo with best supportive care (median OS, 8.5 vs 7.3 months, respectively; HR, 0.71; 95% CI, 0.53–0.95; P=.0199; median PFS 2.8 vs 1.6 months, respectively; HR, 0.45; 95% CI,

0.34–0.60; P<.0001). A pooled analysis of results from REACH and REACH-2, including 542 patients with disease progression on or after sorafenib who had a baseline AFP level of  $\geq$ 400 ng/mL, showed that median OS was greater for patients who received ramucirumab compared with patients who received the placebo (8.1 vs 5.0 months, respectively; HR, 0.69; 95% CI, 0.57–0.84; P=.0002).<sup>238</sup> Post hoc analyses of the REACH and REACH-2 trials revealed the importance of AFP as a prognostic factor as the AFP response was significantly higher in patients treated with ramucirumab compared with placebo (P<.0001).<sup>239</sup> An AFP response was associated with significantly improved survival (13.6 vs 5.6 months; HR, 0.45; P<.0001).<sup>239</sup>

Nivolumab, an anti-PD-1 antibody, was assessed in the phase I/II nonrandomized multi-institution Check-Mate 040 trial, which included 48 patients with advanced HCC in a dose-escalation phase and 214 patients in a dose-expansion phase.<sup>240</sup> In patients treated with nivolumab 3 mg/kg, the objective response rate was 20% for patients in the dose-expansion phase and 15% for patients in the dose-escalation phase. The disease control rates were 64% and 58% for patients in these phases, respectively. Nine-month OS for patients in the dose-expansion phase was 74%. In the dose-escalation phase, 25% of patients had grade 3 or 4 treatment-related adverse events. In the dose-expansion phase, analyses of 57 patients without viral hepatitis who progressed after sorafenib showed a disease control rate of 61%. Median OS and 6month OS rates for these patients were 13.2 months and 75%, respectively. Additional analyses from this trial, published in an abstract, showed a median duration of response of 17 months in sorafenib-naïve patients (n=80) and 19 months in patients who had been previously treated with sorafenib (n=182). Eighteen-month OS rates for these patients were 57% and 44%, respectively.<sup>241</sup>

Based on the results from the CheckMate 040 trial, the FDA gave accelerated approval for nivolumab in 2017 for patients with HCC who progressed on or after sorafenib. These preliminary data led to the confirmatory CheckMate 459, a randomized phase III trial comparing nivolumab to sorafenib in the frontline treatment of advanced HCC.242 In the published abstract by Yau et al, the median OS with nivolumab versus sorafenib was 16.4 versus 14.7 months, respectively (HR, 0.85; P=.075) but the ORR was 15% versus 7%.242 As nivolumab demonstrated meaningful improvements, it has maintained its accelerated FDA approval. Additionally, combination treatment with nivolumab and the CTLA-4 antibody ipilimumab in 148 patients with advanced HCC who were previously treated with sorafenib led to improved clinical responses.<sup>243</sup> The results showed a response rate of 32%, per RECIST version 1.1 as assessed by blinded independent central review, and a median OS of 22.8 months. The results from a long-term follow-up of at least 44 months,

published in an abstract, demonstrated that durable responses were achieved and the median OS was maintained at 22.2 months.<sup>244</sup>

Pembrolizumab, another anti-PD-1 antibody, was assessed in the nonrandomized, open-label, phase II KEY-NOTE-224 trial, which included 104 patients with HCC who progressed on or were intolerant to sorafenib.<sup>245</sup> About 17% of patients had an objective response (all partial responses except for 1 patient who had a complete response), 44% had stable disease, and 33% had progressive disease. Median duration of response was not reached, and, at the time of publication, assessment was ongoing in 12 of the 18 responders. The safety profile was similar to that seen for this drug in other tumor types. Based on these results, the FDA granted accelerated approval for pembrolizumab for patients with HCC who were previously treated with sorafenib. However, the phase 3 KEYNOTE-240 trial comparing pembrolizumab to a placebo in second-line HCC did not meet its primary endpoints (OS and PFS), based on the rigorous statistical plan.<sup>246</sup> Updated data from the KEYNOTE-240 trial, published in an abstract, showed that the median OS with pembrolizumab versus placebo was 13.9 vs 10.6 months, respectively (HR, 0.77) and the median PFS was 3.3 vs 2.8 months, respectively (HR, 0.70).<sup>247</sup> Also, a clinically meaningful difference in ORR was seen favoring pembrolizumab (18.3% vs 4.4%), and the median duration of response on pembrolizumab was 13.9 months. Pembrolizumab has maintained its accelerated approval in patients previously treated with sorafenib. Pembrolizumab can be considered for microsatellite instability-high tumors.248 The NCCN Guidelines include nivolumab, combined nivolumab and ipilimumab, and pembrolizumab as other recommended regimens.

## Management of Resectable Disease

The consensus of the panel is that initial treatment with either partial hepatectomy or transplantation should be considered for patients with liver function characterized by a Child-Pugh class A score, lack of portal hypertension, and who fit UNOS criteria. In addition, patients must have operable disease on the basis of performance status and comorbidity.

Hepatic resection is a potentially curative treatment option and is the preferred treatment of patients with the following disease characteristics: adequate liver function (Child-Pugh class A and selected Child-Pugh class B patients without portal hypertension), solitary mass without major vascular invasion, and adequate liver remnant. Ablation may be considered in patients with tumors <3 cm in diameter who are not resection candidates due to age or comorbidity. The presence of extrahepatic metastasis is considered to be a contraindication for resection. Hepatic resection is controversial in patients

with limited multifocal disease as well as those with major vascular invasion. Liver resection in patients with major vascular invasion should only be performed in highly selected situations by experienced teams.

Transplantation should be considered for patients who meet the UNOS criteria (AFP level ≤1,000 ng/mL and radiologic evidence of either a single lesion >2 cm and <5 cm in diameter, or 2 or 3 lesions >1 cm and <3 cm in diameter, and no evidence of macrovascular involvement or extrahepatic disease) or can be downstaged to within Milan Criteria. Transplant also provides a curative intent option for patients with Child-Pugh class B and C cirrhosis who would not otherwise be surgical candidates. The guidelines have included consideration of bridge therapy as clinically indicated for patients eligible for liver transplant. Patients with tumor characteristics that are marginally outside of the UNOS guidelines may be considered for transplantation at select institutions. Additionally, transplantation can be considered for patients who have undergone successful downstaging therapy (ie, tumor currently meeting Milan criteria). If transplant is not feasible, the panel recommends hepatic resection for this group of patients.

## Surveillance

Although data on the role of surveillance in patients with resected HCC are very limited, recommendations are based on the consensus that earlier identification of disease, primary or recurrent, may facilitate patient eligibility for investigational studies or other forms of life-prolonging treatment. The panel recommends ongoing surveillance—specifically, multiphasic, cross-sectional imaging of the chest, abdomen, and pelvis every 3 to 6 months for 2 years, then every 6 to 12 months after definitive therapies; surveillance may be required indefinitely for patients with ongoing risk for developing a new HCC diagnosis thereafter, such as patients with cirrhosis and/or chronic HBV. Multiphasic cross-sectional imaging (ie, CT or MRI) is the preferred method for surveillance following treatment because of its reliability in assessing arterial vascularity,19 which is associated with increased risk of HCC recurrence following treatment.<sup>251,252</sup> Elevated AFP levels are associated with poor prognosis after treatment 112,253,254 and should be measured every 3 months for 2 years, then every 6 to 12 months after definitive therapies, and depending on risk factors for developing a new HCC thereafter. Re-evaluation according to the initial workup should be considered in the event of disease recurrence. Early imaging per local protocol can be considered.

## Management of Advanced Disease

Locoregional therapy (ablation, arterially directed therapies, or EBRT) is the preferred treatment option for selected patients with unresectable or inoperable liverconfined disease. Based on clinical experience with non-transplant candidates, the panel considers locoregional therapy to be the preferred approach for treating patients with unresectable liver-confined disease, or for those patients with localized tumors who are medically inoperable due to comorbidity. This may include older patients, particularly those with comorbidities or compromised performance status. 115,255,256

Systemic therapy is also recommended for patients with advanced disease, especially for those progressing on locoregional therapies and for those with extrahepatic metastatic disease. Biopsy may be considered for histologic confirmation prior to initiation of treatment. The combination of atezolizumab plus bevacizumab is the preferred category 1 first-line systemic therapy option for patients with Child Pugh A liver function based upon significant survival improvement in the IMBrave150 trial.<sup>231</sup> Sorafenib and lenvatinib are listed as other recommended options for first-line systemic therapy. Sorafenib is recommended as a category 1 option (for selected patients with Child-Pugh class A liver function) and as a category 2A option (for selected patients with Child-Pugh class B7 liver function) with disease characterized as: unresectable (liver-confined) and extensive/not suitable for liver transplantation; local disease only in patients who are not operable due to performance status or comorbidity; or metastatic disease. The panel recommends caution when considering use of sorafenib in patients with elevated bilirubin levels.<sup>257</sup> First-line lenvatinib is also included as a category 1 option for patients with Child-Pugh class A liver function only. FOLFOX is another first-line option, but this is a category 2B option due to the panel's concern regarding the control arm used in this study (doxorubicin) and lack of significant survival benefit in final analysis.<sup>258</sup>

The panel now recommends several subsequent-line therapy options for patients with Child-Pugh A liver disease progression after first-line systemic therapy. However, it should be noted that it is unclear what the benefits of these systemic therapy options are for patients who receive the atezolizumab and bevacizumab regimen as a first-line treatment option and what subsequent agents to use if the disease progresses. Category 1 targeted therapy options include regorafenib, cabozantinib, and ramucirumab. Regorafenib and cabozantinib are recommended only for patients with Child-Pugh A liver function, while ramucirumab is recommended only for patients with a baseline AFP level of 400 ng/mL or greater. Checkpoint inhibitors options include nivolumab monotherapy, pembrolizumab monotherapy, and combination therapy

with nivolumab and ipilimumab. The panel recommends nivolumab as an option for patients with Child-Pugh A or B liver function. Combined nivolumab and ipilimumab are recommended for patients with Child-Pugh A. Based on data from the negative phase III KEYNOTE-240 trial showing that pembrolizumab did not meet its primary endpoints (OS and PFS), the panel changed its recommendation of this drug from category 2A to category 2B for patients with Child-Pugh class A liver function.

The relatively rapid development of these numerous treatment options has made it difficult to address the important question of sequencing them, other than for those that have been approved for use in patients with disease progression on or following sorafenib. Sorafenib may be used in patients with disease progression on or following first-line lenvatinib (Child-Pugh class A or B7 liver function only), but there are currently no data to support the use of lenvatinib for patients with disease progression after sorafenib.

For all patients with advanced stages of HCC treated with systemic therapies, the panel recommends periodic response assessment with cross-sectional imaging of sites at risk for metastatic progression, including chest, multiphase abdomen, and pelvis. In patients with elevated AFP tumor marker at start of therapy, AFP changes on treatment have shown association with treatment response and survival.<sup>235,239,261</sup>

The panel recommends that best supportive care measures be administered to patients with unresectable or metastatic disease, alongside cancer-directed therapies.

## **Conclusions**

Although HCC has traditionally had limited therapeutic options and carried a poor prognosis, a multipronged approach involving the collaboration of multiple specialties is improving outcomes in this disease. The panel recommends screening of high-risk patients to allow for early detection and performing multiphasic imaging for accurate diagnosis and pathologic confirmation where indicated. The panel also recommends multidisciplinary evaluation to optimize management given the multiple surgical, liver-directed, and systemic therapy options availabel for patients. Finally, with multiple FDA-approved systemic therapy regimens for unresectable and metastatic HCC, the panel recommends careful consideration of liver function, prior therapies, and co-morbidities in selecting and sequencing systemic therapy.

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The NCCN Guidelines Staff have no conflicts to disclose.

\*The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:

Anne M. Covey, MD: Amgen Inc.