REVIEW ARTICLE

CURRENT CONCEPTS

Hepatocellular Carcinoma

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Each year, hepatocellular carcinoma is diagnosed in more than half a million people worldwide, including approximately 20,000 new cases in the United States.[1,2] Liver cancer is the fifth most common cancer in men and the seventh in women. Most of the burden of disease (85%) is borne in developing countries, with the highest incidence rates reported in regions where infection with hepatitis B virus (HBV) is endemic: Southeast Asia and sub-Saharan Africa (Fig. 1).[3] Hepatocellular carcinoma rarely occurs before the age of 40 years and reaches a peak at approximately 70 years of age. Rates of liver cancer among men are two to four times as high as the rates among women. Hepatocellular carcinoma related to infection with hepatitis C virus (HCV) has become the fastest-rising cause of cancer-related death in the United States, and during the past two decades, the incidence of hepatocellular carcinoma in the United States has tripled while the 5-year survival rate has remained below 12%[2] (Fig. 2). The greatest proportional increase in cases of hepatocellular carcinoma has been seen among Hispanics and whites between 45 and 60 years of age.[4]

Risk Factors

Major risk factors for hepatocellular carcinoma include infection with HBV or HCV, alcoholic liver disease, and most probably nonalcoholic fatty liver disease. Less common causes include hereditary hemochromatosis, alpha$_1$-antitrypsin deficiency, autoimmune hepatitis, some porphyrias, and Wilson's disease. The distribution of these risk factors among patients with hepatocellular carcinoma is highly variable, depending on geographic region and race or ethnic group.[5] Most of these risk factors lead to the formation and progression of cirrhosis, which is present in 80 to 90% of patients with hepatocellular carcinoma. The 5-year cumulative risk for the development of hepatocellular carcinoma in patients with cirrhosis ranges between 5% and 30%, depending on the cause (with the highest risk among those infected with HCV), region or ethnic group (17% in the United States and 30% in Japan), and stage of cirrhosis (with the highest risk among patients with decompensated disease).[6]

Worldwide, chronic HBV infection accounts for approximately 50% of all cases of hepatocellular carcinoma and virtually all childhood cases. In endemic areas in Asia and Africa, where HBV infection is transmitted from mother to newborn, up to 90% of infected persons have a chronic course, with frequent integration of HBV into host DNA. Although HBV can cause hepatocellular carcinoma in the absence of cirrhosis, the majority (70 to 80%) of patients with HBV-related hepatocellular carcinoma have cirrhosis. The risk of hepatocellular carcinoma among persons with chronic HBV infection (those who are positive for the hepatitis B surface antigen [HBsAg]) is further increased if they are male or elderly, have been infected for a long time, have a family history of hepatocellular carcinoma, have been exposed to the mycotoxin aflatoxin, have used alcohol or tobacco, are coinfected with HCV or hepatitis delta virus, have high levels of HBV hepatocellular replication (as indicated

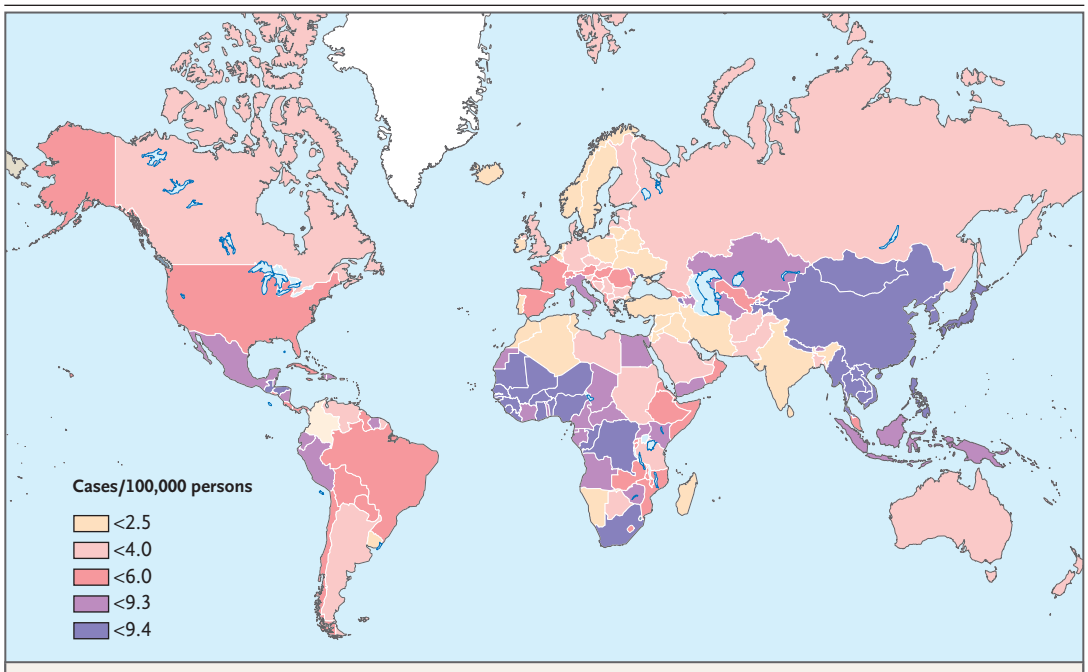

Figure 1. Regional Variation in the Estimated Age-Standardized Incidence Rates of Liver Cancer.
The incidence rates shown (numbers of cases per 100,000 persons) pertain to both sexes and all ages. Adapted from the World Health Organization.[3]

by high levels of HBV DNA),[7] or are infected with HBV genotype C.[8] HBV DNA can also be detected in persons who are HBsAg-negative, but the association with risk of hepatocellular carcinoma is unclear in these cases.

The estimated risk of hepatocellular carcinoma is 15 to 20 times as high among persons infected with HCV as it is among those who are not infected, with most of the excess risk limited to those with advanced hepatic fibrosis or cirrhosis.[9] HCV infection occurred in large numbers of young adults in Japan in the 1920s, in southern Europe in the 1940s, and in North America in the 1960s and 1970s (with the cases in North America resulting from the sharing of contaminated needles by users of injection drugs and from blood transfusions).[10] Markers of HCV infection are found in 80 to 90% of patients with hepatocellular carcinoma in Japan, 44 to 66% in Italy, and 30 to 50% in the United States.[5] It has been projected that cases of HCV-related hepatocellular carcinoma will continue to increase in the United States over the next two to three decades. Risk factors for hepatocellular carcinoma among persons infected with HCV include an older age at the time of infection, male sex, coinfection with the human immunodeficiency virus or HBV, and probably diabetes or obesity.[11-13] Prolonged, heavy use of alcohol (defined as daily ingestion of 40 to 60 g of alcohol, with a standard drink containing 13.7 g, or 0.6 oz) is a well-established risk factor for hepatocellular carcinoma both independently (with the risk increased by a factor of 1.5 to 2.0) and in combination with HCV infection and, to a lesser extent, with HBV infection.[9]

In several studies conducted in Western countries, 30 to 40% of patients with hepatocellular carcinoma did not have chronic infection with HBV or HCV, suggesting the presence of other causes of disease. Some of these patients were more likely to have had clinical or biochemical features of fatty liver disease (obesity) or the metabolic syndrome (e.g., type 2 diabetes). In population-based cohort studies in the United States, Scandinavia, Taiwan, and Japan,[12-14] hepatocellular carcinoma was 1.5 to 2.0 times as likely to develop in obese persons as in those who were not obese. Several case–control studies and a few cohort studies have shown that, on average, hepatocellular carcinoma is twice as likely to develop in persons with type 2 diabetes as compared with those who do not have diabetes.[15,16] Nonalcoholic fatty liver disease, which is present in up to 90% of all obese persons and up to 70% of persons with

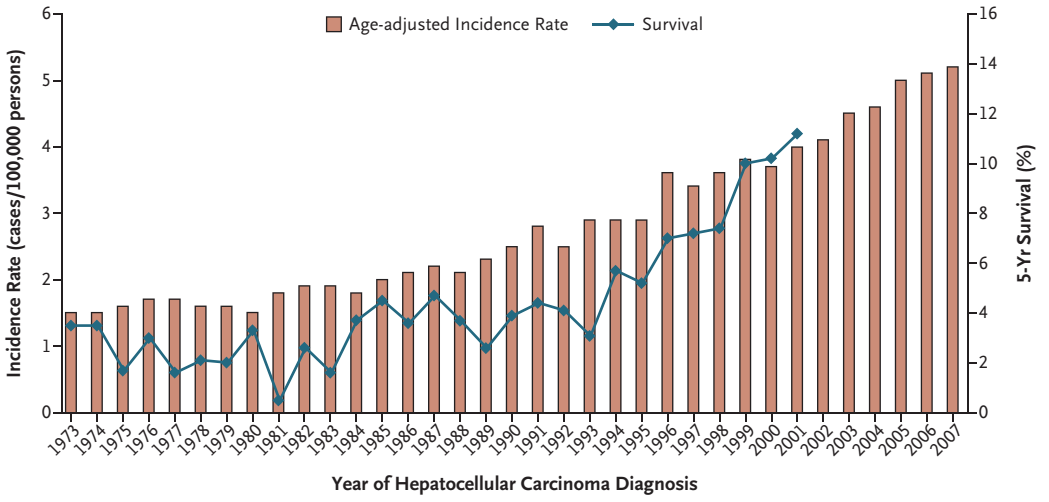

Figure 2. Age-Adjusted Incidence and 5-Year Survival Rates for Patients with Hepatocellular Carcinoma in the United States, 1973–2007.

type 2 diabetes, has been proposed as a possible risk factor for hepatocellular carcinoma.[17] Because of the paucity of data showing a direct association between progression of fatty liver disease and hepatocellular carcinoma, currently available estimates of risk are unclear. However, given the very high prevalence of the metabolic syndrome in the United States, even small increases in risk related to obesity or diabetes could translate into a large number of cases of hepatocellular carcinoma.

Several case–control and cohort studies conducted in Japan and southern Europe have shown that coffee drinking is associated with a reduced risk of hepatocellular carcinoma.[18] The mechanisms for this possible protective effect have not been established. Coffee drinking has also been associated with reduced insulin levels and a reduced risk of type 2 diabetes.[19]

PREVENTION

HBV VACCINATION

A safe and effective HBV vaccine is available and should be given to all newborns and persons without immunity who are at high risk for infection. National HBV vaccination programs have dramatically reduced the prevalence of HBV infection, and there has been a concomitant decrease in the incidence of hepatocellular carcinoma. In Taiwan, for example, the first universal HBV vaccination program for newborns began 20 years ago, with infants of mothers at high risk for HBV infection (HBsAg-positive) receiving both the vaccine and an injection of hepatitis B immune globulin. Since the program began, the incidence of hepatocellular carcinoma in children between 6 and 14 years of age has fallen by 65 to 75%.[20]

ANTIVIRAL TREATMENT

There is moderately strong evidence that antiviral therapy that controls HBV infection in HBsAg-positive patients and that eradicates HCV in patients with viremia substantially reduces but does not eliminate the risk of hepatocellular carcinoma in patients with viral hepatitis. In one large, rigorous, Chinese study, patients with chronic HBV infection who also had cirrhosis or advanced fibrosis were randomly assigned to receive 100 mg of lamivudine per day or placebo for up to 5 years; the incidence of hepatocellular carcinoma was significantly reduced in the lamivudine group as compared with the placebo group (3.9% vs. 7.4%; hazard ratio, 0.49; $P=0.047$).[21] Lower-quality evidence, from nonrandomized trials and observational studies, suggests that there is a reduction in the risk of disease with either interferon or lamivudine.[22]

The results of one randomized, controlled study and several nonrandomized studies involving patients who were infected with HCV but did not have cirrhosis indicated that among those treated with interferon-based therapy who had a sustained

viral response, the risk of hepatocellular carcinoma was reduced by 57 to 75%.[23,24] Another study showed that among patients with HCV infection who did have cirrhosis and did not have a sustained response to antiviral therapy, the risk of hepatocellular carcinoma was not significantly reduced with maintenance interferon therapy.[25]

SURVEILLANCE

Practice guidelines from the American Association for the Study of Liver Diseases recommend surveillance for patients at high risk for hepatocellular carcinoma.[26] Collectively, the strength of the evidence supporting the efficacy of surveillance in high-risk groups is modest. One randomized, controlled trial of nearly 19,000 HBV-infected patients in China showed that surveillance consisting of measurement of serum alpha-fetoprotein levels and ultrasonographic imaging every 6 months was associated with a 37% reduction in mortality related to hepatocellular carcinoma.[27] However, another randomized, controlled trial involving HBV-positive patients in China showed that surveillance was not beneficial.[28] There are no data from randomized trials of surveillance in patients with HCV or in patients with cirrhosis. Several nonrandomized trials and observational studies have shown a survival benefit in patients with small hepatocellular tumors, but these studies had unavoidable biases.[29,30]

I recommend ultrasonography of the liver combined with measurement of serum alpha-fetoprotein levels every 6 to 12 months as surveillance for hepatocellular carcinoma in patients with cirrhosis or advanced hepatic fibrosis, irrespective of the cause. Both are also useful in surveillance of HBV carriers with or without cirrhosis if they are Africans older than 20 years of age or Asians older than 40 years of age or if they have a family history of hepatocellular carcinoma. Because hepatocellular carcinoma is rare in HCV-infected patients with mild or no hepatic fibrosis, surveillance is not recommended for this group. With a cutoff point of 20 ng per milliliter, serum levels of alpha-fetoprotein have low sensitivity (25 to 65%) for the detection of hepatocellular carcinoma and are therefore considered inadequate as the sole means of surveillance. Ultrasonography has a sensitivity of approximately 65% and a specificity of more than 90% for early detection.[31] The calls for abandoning the monitoring of alpha-fetoprotein levels may be premature,[32] especially given the already low rates of surveillance of hepatocellular carcinoma in community practice. In North American studies, the combined measurement of alpha-fetoprotein and other biomarkers, such as des-gamma-carboxyprothrombin or lectin-bound alpha-fetoprotein, was shown to provide only a limited additional benefit as compared with the measurement of alpha-fetoprotein alone and thus cannot be recommended.[30,33,34]

Computed tomography (CT) and magnetic resonance imaging (MRI) are not generally recommended for hepatocellular carcinoma surveillance (as distinct from diagnosis and staging); their sensitivity, specificity, and positive and negative predictive values for this purpose are unknown, and their use is associated with high cost as well as possible harm (e.g., radiation, allergic reaction to contrast medium, nephrotoxicity with CT, and nephrogenic fibrosing dermopathy from the use of gadolinium with MRI in patients with renal insufficiency).

DIAGNOSIS

The diagnosis of hepatocellular carcinoma can increasingly be made with the use of noninvasive imaging tests, especially at specialized centers. In patients with cirrhosis and a focal hepatic mass larger than 2 cm in diameter, the diagnosis can be confidently established on the basis of the presence of typical imaging features showing areas of early arterial enhancement and delayed washout (less enhancement than the rest of the liver) in the venous or delayed phase of four-phase multidetector CT (the four phases are unenhanced, arterial, venous, and delayed) or in dynamic contrast-enhanced MRI (Fig. 3). These radiologic changes are related to increased vascularity in the hepatocellular carcinoma, supplied by the hepatic artery. For lesions 1 to 2 cm in diameter, concordant findings from CT and MRI are recommended in order to diagnose hepatocellular carcinoma with confidence. In these patients, an alpha-fetoprotein level of 400 ng per milliliter or higher is also highly predictive of hepatocellular carcinoma.

Image-guided biopsy should be considered for focal hepatic masses with atypical imaging features or discrepant findings on CT and MRI, or for lesions detected in the absence of cirrhosis. A negative biopsy result, although reassuring, does not rule out malignant disease; the nodule should be further studied at intervals of 3 to 6 months until it disappears, grows larger, or displays char-

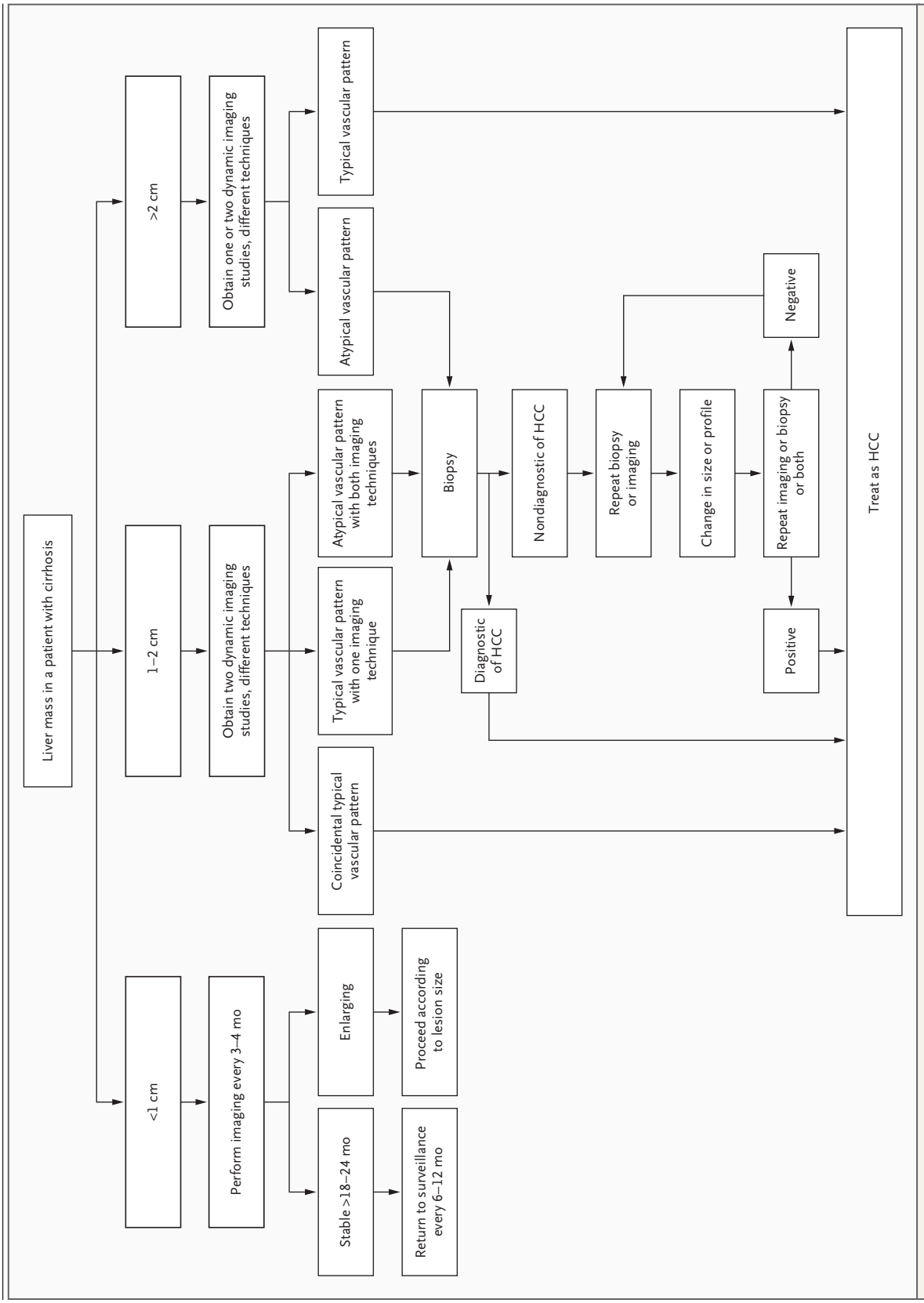

Figure 3. Proposed Procedure for the Diagnostic Evaluation of a Liver Mass in a Patient with Cirrhosis.
Adapted from Bruix and Sherman.[26] HCC denotes hepatocellular carcinoma.

acteristics that are diagnostic of hepatocellular carcinoma.[26] The risk of tumor seeding along the needle track after biopsy in patients with suspected hepatocellular carcinoma is low (2.7%).[35] Accurate assessment of liver nodules measuring less than 1 cm is difficult, whether imaging alone or imaging and biopsy are performed; these lesions are probably best monitored with the use of ultrasonography at intervals of 3 to 6 months for 1 to 2 years.

TREATMENT

STAGING-GUIDED TREATMENT

There are several potentially curative or palliative approaches to the treatment of hepatocellular carcinoma.[36] The choice of treatment is driven by the cancer stage, the resources available, and the level of practitioner expertise. Since only a few randomized, controlled trials have compared these approaches, most recommendations for staging-guided treatment rely on the findings of observational studies or expert opinion. Numerous staging systems for hepatocellular carcinoma have been developed, and they have been validated to varying degrees. Barcelona Clinic Liver Cancer (BCLC) staging has been proposed as the standard means of assessing the prognosis for patients with hepatocellular carcinoma. The BCLC staging system is a useful assessment tool that incorporates data on the patient's performance status, number and size of nodules, cancer symptoms, and liver function as determined by the Child–Pugh classification system.[37] The Child–Pugh scoring system uses five clinical measures of liver disease. Each measure is assigned a score of 1 to 3 points, with 3 points indicating the most severe derangement. Scores on the five measures are then summed to determine the overall severity of disease, with a sum of 5 or 6 points indicating class A disease, 7 to 9 points class B, and 10 to 15 points class C, or the most severe disease. (For additional details on the Child–Pugh scoring system, see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Although genomic analysis has been used to identify possible prognostic biomarkers,[38] the results require validation. High serum and tissue levels of vascular endothelial growth factor are significantly associated with poor survival,[39] but the usefulness of this biomarker in clinical practice is unclear.

Very-early-stage hepatocellular carcinoma is currently difficult to diagnose, since it requires presentation with a single, asymptomatic lesion measuring less than 2 cm in diameter, with no vascular or distant metastases (Fig. 4). Surgical resection in these cases is associated with an overall survival rate of 90%. For patients presenting with early-stage hepatocellular carcinoma who have some preserved liver function (falling within class A or B of the Child–Pugh system) with a solitary hepatocellular-carcinoma nodule measuring less than 5 cm in diameter or no more than three nodules, each measuring less than 3 cm in diameter, the choice of therapy is dictated by the severity of the liver dysfunction, the extent of portal hypertension, and the patient's status with respect to coexisting conditions. Surgical resection should be considered for patients with solitary tumors and no portal hypertension. Otherwise, the most appropriate treatment for patients with early-stage hepatocellular carcinoma is liver transplantation, which is associated with a 5-year survival rate of up to 75%. If transplantation is not possible, local ablation is the next best option.

Patients with compensated cirrhosis, no symptoms related to hepatocellular carcinoma, and no vascular invasion but with large or multifocal lesions are considered to have intermediate-stage hepatocellular carcinoma. In these patients, transarterial chemoembolization (TACE) improves the 2-year survival rate by 20 to 25% as compared with more conservative therapy.

Patients with mild cancer-related symptoms, vascular invasion, or extrahepatic spread are considered to have advanced-stage disease and are not suitable candidates for radical therapies. TACE has increased the survival rate among well-selected candidates, but the primary treatment option for patients with this stage of disease is the oral chemotherapeutic agent sorafenib. Patients with terminal-stage disease present with cancer symptoms related to liver failure, vascular involvement, or extrahepatic spread. The 1-year survival rate for such patients is less than 10%, and they do not benefit from the treatments mentioned above.[36] (A chart that provides an overview of disease stages and recommended treatments is provided in the Supplementary Appendix.)

SURGICAL RESECTION

Surgical resection is the treatment of choice in patients without cirrhosis who are in the very early stage of hepatocellular carcinoma. For patients

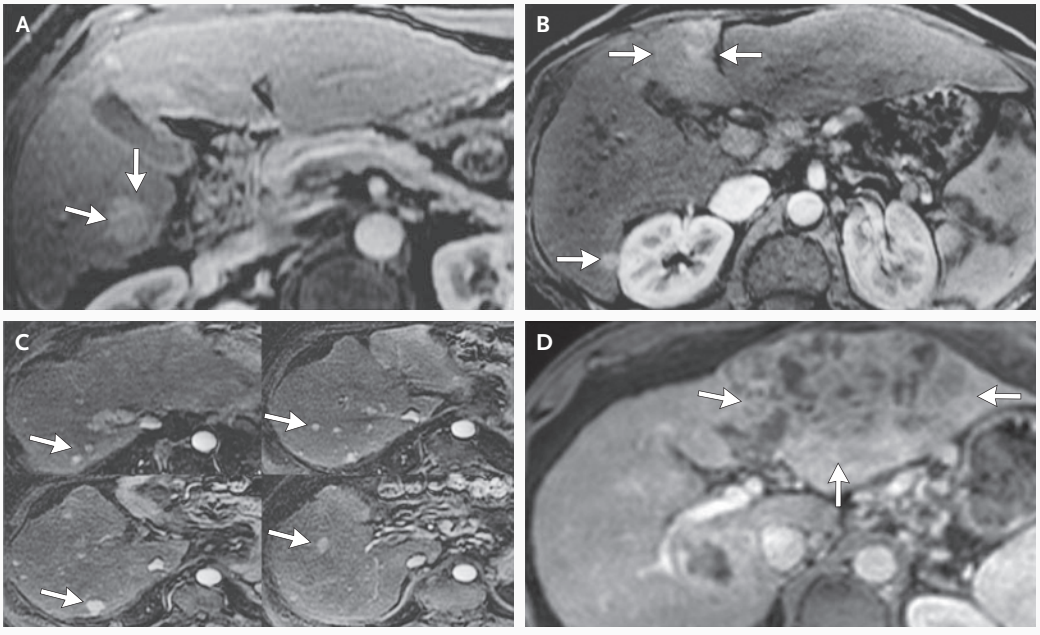

Figure 4. MRI Studies Showing the Effects of Hepatocellular Carcinoma at Different Stages of the Disease.

All MRI studies were performed with the use of intravenous contrast material and show areas of enhancement typically found in patients with hepatocellular carcinoma. Panel A shows a single mass measuring 1.7 cm in diameter (arrows), indicating very-early-stage hepatocellular carcinoma (defined as a single lesion measuring less than 2 cm in diameter). Panel B shows two lesions, measuring 2.4 and 1.2 cm in diameter (arrows), indicating early-stage hepatocellular carcinoma (defined as fewer than three nodules, each measuring less than 3 cm in diameter). Panel C shows multiple hepatocellular-carcinoma nodules (arrows) in a patient with Child–Pugh class B cirrhosis, indicating intermediate-stage disease. Panel D shows a large mass (more than 10 cm in diameter) and ascites (arrows), indicating advanced-stage hepatocellular carcinoma.

with cirrhosis, resection produces the best results when the tumor is small (<3 cm in diameter), portal hypertension (a hepatic venous pressure gradient >10 mm Hg) is absent, and the total bilirubin level is normal (≤1 mg per deciliter [≤17.1 μmol per liter]).[40,41] The 5-year risk of recurrence of hepatocellular carcinoma after resection is as high as 70% because the underlying chronic liver disease continues to put the patient at risk for the development of new hepatocellular carcinoma. In the United States, less than 5% of patients are candidates for hepatic resection. This approach is much more common in Asian countries, where there are greater numbers of young people with HBV-related hepatocellular carcinoma and no or minimal cirrhosis.

LIVER TRANSPLANTATION

Among patients with hepatocellular carcinoma who have underlying cirrhosis, orthotopic liver transplantation in selected candidates is the treatment option associated with the lowest risk of tumor recurrence. Other treatment options carry a higher long-term risk of recurrence because they have no effect on chronic liver disease, which is the major driving factor in the development of hepatocellular carcinoma. However, because of the scarcity of organs available for transplantation within an optimal time frame, strict criteria are used to limit transplantation to patients with hepatocellular carcinoma who are likely to have excellent outcomes.

Patients with hepatocellular carcinoma who meet the Milan criteria for orthotopic liver transplantation (essentially, a solitary nodule measuring less than 5 cm in diameter or three nodules, each measuring less than 3 cm) have an expected 4-year overall survival rate of 85% and a recurrence-free survival rate of 92%.[42] In the United States, experience in clinical practice supports the effectiveness of orthotopic liver transplantation in patients meeting the Milan criteria as adopted by the United Network for Organ Sharing (UNOS).[43]

The primary criteria used by UNOS to prioritize the allocation of livers available for transplantation are the Model for End-Stage Liver Disease (MELD) criteria (Table 2 in the Supplementary Appendix). The MELD criteria are based on a scoring system that uses the values for total bilirubin level, creatinine level, and international normalized ratio to assess the severity of chronic liver disease. However, these criteria were not developed to predict the risk of death among patients with chronic liver disease who also have hepatocellular carcinoma. Therefore, patients with hepatocellular carcinoma who have been placed on the list for liver transplantation are eligible for additional MELD points. The number of patients with hepatocellular carcinoma who have received transplants has increased considerably since the adoption of the MELD criteria in 2001.

Criteria developed at the University of San Francisco (UCSF) have been put forward to expand eligibility for liver transplantation among patients with hepatocellular carcinoma beyond that allowed by the Milan criteria. To meet the UCSF criteria for orthotopic liver transplantation, a patient must have a solitary hepatocellular carcinoma measuring up to 6.5 cm in diameter or up to three lesions, each measuring no more than 4.5 cm in diameter, with a total combined measurement of less than 8 cm.[44] Although several observational studies of intermediate quality have shown no significant differences in survival rates among patients deemed eligible for transplantation according to the Milan criteria as compared with those deemed eligible according to the UCSF criteria, the UNOS has not adopted the UCSF criteria because of the limited availability of organs. When a patient does not meet either the Milan or the UCSF criteria for transplantation, some institutions provide treatment with TACE or radiofrequency ablation, with the goal of downstaging the condition to improve the patient's eligibility for transplantation. This strategy has met with variable success and remains an area of investigation.[45] (Table 2 in the Supplementary Appendix provides detailed information on the MELD, Milan, and UCSF criteria.)

LOCAL ABLATION

Radiofrequency ablation has become the most frequently used form of local ablation therapy. It is the best treatment alternative for patients with early-stage hepatocellular carcinoma who are not eligible for surgical resection or transplantation. Several recent randomized trials of adequate quality have shown radiofrequency ablation to be more effective than the once-conventional method of ethanol injection in treating patients with small hepatocellular tumors (2 to 3 cm in diameter), with lower rates of local recurrence and higher rates of overall and disease-free survival.[46] Short-term outcomes are excellent, with overall survival rates of 100% and 98% at 1 and 2 years, respectively, but long-term outcomes are consistent with the noncurative nature of radiofrequency ablation, with 5-year recurrence rates as high as 70%. The results of two randomized, controlled trials comparing radiofrequency ablation and surgical resection showed no significant differences in overall or recurrence-free survival; as expected, radiofrequency ablation was associated with lower rates of complications and hospitalization.[47,48]

TRANSARTERIAL CHEMOEMBOLIZATION AND RADIOEMBOLIZATION

TACE has been shown to improve survival among patients with preserved liver function, particularly those with Child–Pugh class A cirrhosis who do not have extrahepatic metastases, vascular invasion, or prominent cancer-related symptoms. A meta-analysis of randomized, controlled trials assessing the use of arterial embolization, chemoembolization, or both as primary palliative treatment for hepatocellular carcinoma showed that these procedures were associated with an improved 2-year survival rate as compared with conservative treatment.[49] TACE is also used as a neoadjuvant therapy or as a means of downstaging a patient's condition before liver transplantation, but whether these approaches provide a survival benefit is unclear. A postembolization syndrome of fever and abdominal pain related to hepatic ischemia occurs in up to 50% of patients treated with TACE. Embolization should not be performed without the use of a chemotherapeutic agent; there are few data to guide the choice of the chemotherapeutic agent or the retreatment schedule, which in practice ranges from 2 to 5 sessions. In recent randomized, controlled trials,[50,51] the use of a drug-eluting bead that releases the drug in a controlled fashion during TACE has been shown to be associated with a reduction in both hepatic and systemic side effects and with an increase in local tumor response.

Radioembolization with yttrium-90 microspheres has recently been used as palliative treatment for patients with Child–Pugh class A cirrhosis and intermediate-stage hepatocellular carcinoma.[52] However, there have been no con-

trolled trials comparing yttrium-90 radioembolization with TACE or with other types of treatment.

TARGETED MOLECULAR THERAPY

Until recently, no systemic chemotherapy was shown to be consistently efficacious in treating hepatocellular carcinoma. Sorafenib is a small-molecule multikinase inhibitor that is administered orally and has antiproliferative and antiangiogenic properties. In recent randomized, controlled trials, it has been associated with a 37% increase in overall survival (equivalent to a gain of 2 to 3 months of life), as compared with placebo, in patients with advanced hepatocellular carcinoma and compensated cirrhosis.[53] Rash on the hands and feet, diarrhea, and fatigue are the most commonly reported side effects. The relative success with sorafenib has prompted increased interest in evaluating its use alone or in combination with other treatments (e.g., TACE) during other stages of disease and the development and testing of other targeted molecular medications. Other small molecules, such as brivanib and erlotinib, and monoclonal antibodies, such as bevacizumab and cetuximab, are currently being studied in patients with hepatocellular carcinoma.

TRANSLATING EFFICACY INTO EFFECTIVENESS

Despite encouraging reports on clinical trials and studies from referral centers regarding the efficacy of antiviral therapy for infection with HBV or HCV and of the surveillance and treatment of hepatocellular carcinoma, their effectiveness in clinical practice is low. The proportions of patients receiving these interventions and the outcomes are considerably lower in community-based studies than in those from referral centers. For example, in one U.S. population-based study, only 29% of patients who had a diagnosis of hepatocellular carcinoma had undergone annual surveillance in the 3 years before receiving the diagnosis,[54] and in another study, only 13% of patients with HCV-related cirrhosis who were at risk for hepatocellular carcinoma underwent surveillance.[55] Similar studies showed low utilization of transplantation,[56] resection, and TACE.[56] Obstacles to effective care include the difficulty of implementing surveillance that requires repeated assessments over relatively short periods and strategies ensuring prompt recall, the complicated diagnostic evaluation, and the limited availability and high cost of potentially curative therapy. In addition to the development of new biomarkers and drugs, several steps must be taken to improve the outcomes for patients with hepatocellular carcinoma. These include increasing the number of patients who receive a diagnosis in the early or very-early stages of disease through the testing and implementation of surveillance programs, provision of the optimal therapy for individual patients (e.g., drug and alcohol rehabilitation), use of validated staging systems, and perhaps most important, improvement of access to specialized multidisciplinary care.

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Disclosure forms provided by the author are available at NEJM.org.

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