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Extending Survival With the Use of Targeted Therapy in the Treatment of Hepatocellular Carcinoma

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Abstract: Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide, with an increasing incidence projected through 2020. HCC is the third-leading cause of cancer-related deaths worldwide. Management of HCC is complicated by the fact that these patients also have a cirrhotic or otherwise diseased liver that led to the tumorigenesis. To aid in treatment decisions, several staging systems have been developed. In the United States, the Barcelona Clinic Liver Cancer (BCLC) system has emerged as the predominant system, owing to its concomitant consideration of tumor stage, liver function, and physical status, as well as its ability to identify patients with early-stage disease who may benefit from curative therapies. Surveillance for HCC has gained increasing importance in light of several studies demonstrating both clinical and cost benefits. Once HCC is detected and diagnosed, it is usually managed according to its BCLC stage. Patients with early-stage disease often benefit from potentially curative therapies, such as surgical resection and liver transplantation. Often, local ablation such as radiofrequency ablation or percutaneous alcohol injection can be used not only as an effective treatment, but also as a bridge therapy to maintain the status of patients on the liver transplant list. Intermediate-stage patients are typically treated with transarterial chemoembolization, but have a high rate of disease recurrence. The multikinase inhibitor sorafenib is the only treatment option approved for patients with advanced-stage HCC. Sorafenib has demonstrated a significant survival advantage in these patients. Numerous studies have evaluated other novel targeted therapies in this setting, but none have shown superiority to sorafenib.

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Target Audience

This activity has been designed for medical oncologists, gastroenterologists, and hepatologists who treat patients with hepatocellular carcinoma.

Statement of Need/Program Overview

Hepatocellular carcinoma (HCC) is a global health issue, and the incidence of HCC in Western countries is rising due to an increase in the number of related prerequisite diseases, including hepatitis C, diabetes, and nonalcoholic steatohepatitis. Although therapies such as liver transplantation and surgical resection may offer the potential of a cure, these treatment options are available to only a minority of carefully selected patients. Furthermore, each of these modalities is associated with a relatively high risk of recurrence. The need for effective systemic treatment alternatives led to the development of the tyrosine kinase inhibitor sorafenib. Sorafenib is associated with a significant benefit in overall survival among patients with advanced unresectable HCC. Other targeted agents are currently in clinical development for HCC.

Educational Objectives

After completing this activity, the participant should be better able to:

- Evaluate the latest data regarding the efficacy outcomes associated with HCC therapies
- Implement strategies to incorporate new and emerging agents into the treatment of HCC
- Compare the results of clinical trial data of targeted therapy in HCC
- Identify HCC patients in clinical practice who are appropriate candidates for ongoing clinical trials of new and emerging targeted agents

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Overview and Description of Hepatocellular Carcinoma

Richard S. Finn, MD

Any of the multiple cell types that make up the liver can be associated with the development of cancer. The most common liver cancer is hepatocellular carcinoma (HCC), which arises from the hepatocytes. Other tumor types that are categorized as primary liver cancer include bile duct cancer (cholangiocarcinoma) and rare cancers such as angiosarcoma, hemangiosarcoma, and hepatoblastoma. In this report, I will focus on the most common form, HCC.

Epidemiology and Incidence

In the United States, an estimated 30,640 new cases of primary liver cancer are expected to be diagnosed in 2013, the large majority being HCC.[1] While it may be considered uncommon in the United States, its incidence continues to grow. Globally, it is the sixth most common malignancy and the third-leading cause of cancer-related death.[2] The burden of HCC is expected to worsen in the coming years, plateauing between 2015 and 2020.[3]

There appear to be marked variations in the global incidence of liver cancer, with most new cases appearing in developing countries. A 2008 analysis of the worldwide burden of cancer using data from the GLOBOCAN series (published by the International Agency for Research on Cancer) found that almost 85% of liver cancer cases occurred in the developing world.[4] Areas of highest incidence were in Eastern and South-Eastern Asia, Middle and Western Africa, Melanesia, and Micronesia/Polynesia. More than half of the liver cancer cases in the world occur in China; Senegal, Gambia, and South Korea also have high rates of the disease.[5] Reasons for the disproportionate occurrence of HCC in the developing world may include a failure to recognize individuals at high risk for HCC; a higher prevalence of risk factors within the population; a propensity for late diagnosis owing to a lack of medical expertise, facilities, and training; and a lack of effective treatment following diagnosis.[6] Much lower rates of liver cancer are evident in developed regions, such as North and South America, Northern Europe, and Oceania. An exception to this finding is Southern Europe.[4] Interestingly, recent epidemiologic surveys suggest that the risk of liver cancer in certain high-risk countries is beginning to decline, owing primarily to a greater emphasis on vaccination against the hepatitis B virus (HBV).[7,8]

Liver cancer occurs more often in men; worldwide, the overall sex ratio is 2.4 for men versus women. The same trend is evident in the United States, where the male-to-female ratio for liver cancer incidence in 2013 is expected to be 2.87.[1] The higher rates among men may be a reflection of their greater likelihood to be exposed to risk factors for HCC (such as HBV or hepatitis C virus [HCV] infection and alcohol consumption). However, laboratory studies demonstrate that male mice exhibit a higher rate of HCC development, suggesting there may be sex-specific biologic factors that influence HCC development as well.[5]

HCC is the most common primary malignancy in the liver. HCC comprises over 80% of the new liver cancer cases estimated to occur during 2013 in the United States.[1] Other estimates suggest that HCC accounts for up to 90% of primary liver cancers.[5] Thus, the epidemiological trends associated with liver cancer can be considered a general reflection of trends in HCC incidence as compared to other liver malignancies.[2]

Liver cancer is associated with significant mortality and a high fatality rate. The overall ratio of mortality to incidence is 0.93.[4] Due to its poor prognosis, liver cancer is the third-leading cause of cancer-related deaths worldwide, accounting for approximately 696,000 deaths annually.[4] Among men and women in the United States, liver cancer is the fifth-leading and ninth-leading cause of cancer-related deaths, respectively.[1] HCC is the fastest growing cause of cancer-related deaths among men in this country.[5]

Reasons for Rising Incidence

As noted above, the incidence rates of HCC in the United States have historically been lower than global rates. However, some reports have provided evidence that the age-adjusted incidence rates of HCC have doubled in the United States, and the mortality rates due to primary liver cancers have increased more rapidly than any other leading cause of cancer.[9,10] These increases in HCC are not limited to the United States; HCC incidence is also growing throughout Latin America, which was previously noted for its low rates of liver cancer. For example, an examination of HCC epidemiology in Mexico found that general mortality rates for HCC increased from 4.1 per 100,000 in 2000 to 4.7 per 100,000 in 2006.[11]

A cohort analysis of incidence rates was performed with data from 1975–2005.[12] Notably, the age-adjusted incidence rates of HCC tripled between these years, increasing from 1.6 cases per 100,000 to 4.9 cases per 100,000. The best-fitting model for the overall HCC incidence trends during

these years had 2 segments; the first ranged from 1975–1980 and showed no change in HCC incidence, while the second ranged from 1980–2005 and estimated an annual percent change of 4.5% ($P \leq .05$). The patterns in HCC-related mortality showed similar increases, with an annual percent change of 1.6% between 1992 and 2005 ($P \leq .05$). The most notable increases occurred among middle-aged black, Hispanic, and white men.

One explanation for the increasing incidence of HCC in recent decades is the epidemic of HCV infection that occurred during the 1960s.[13] This same epidemic has been proposed as one of the main causes for the marked increase in HCC incidence across southern Europe between 1983 and 1992. Other reasons for the increase in HCC incidence include growing levels of HBV infection, alcohol consumption, obesity, and diabetes.[2] Another factor that has been proposed to account for the rising increase in HCC is the changing patterns of immigration to Europe and North America.[14]

Disease State and Related Conditions

One of the challenges in treating HCC is its occurrence in the background of a cirrhotic liver. Patients with HCC therefore need to be approached as having 2 diseases: a malignancy, and chronic liver disease and its associated complications. As a result, HCC patients often experience significant comorbidities that greatly impact their survival.

The cirrhotic liver can be considered a premalignant organ, in which inflammation, cellular proliferation, or both can lead to genomic instability. Some of the most frequently observed molecular alterations in HCC include loss of altered angiogenesis pathways, changes in cell cycle checkpoints, resistance to apoptosis, and activation of oncogenic cellular survival and proliferation pathways.

In patients without HCC, liver transplantation has a very high success rate in treating chronic liver disease and the resultant complications of cirrhosis. The use of liver transplant in patients with HCC has been well-established for patients with tumor burden according to the Milan Criteria (1 tumor <5 cm, or 3 tumors all <3 cm, with no vascular invasion) with outcomes similar to transplant for patients without HCC.[15] Expanding the role for transplant beyond the Milan criteria remains a controversial topic, as it has become apparent that the success of liver transplantation is dependent upon the tumor burden.[16] This association has led to increasing debate regarding the selection of HCC patients to receive organs against the background of a limited supply of organ donations.

Risk Factors

One of the unique characteristics of HCC is that it almost never develops in a healthy liver; instead, the risk of cancer sharply increases with cirrhosis and chronic liver injury.[5] Although the risk of HCC remains low even among patients with chronic liver disease, it is exponentially increased once cirrhosis sets in. The common causes of liver cirrhosis are considered to be among the key risk factors for HCC. Chief among these is chronic infection with HBV and/or HCV. Chronic HBV infection is estimated to account for 50–80% of HCC cases worldwide.[17] Interestingly, some cases of HCC have been documented to arise in patients with chronic HBV infection even in the absence of cirrhosis. This phenomena is attributed to the ability of the HBV to integrate into the host genome, resulting in transactivation of oncogenes within the host cells.[18] Data suggest that hepatitis B vaccination will play a major role in tempering the rising incidence of HCC in the coming years. Promising data were reported in a study of Taiwanese children who showed a dramatic decline in HCC incidence 10 years after the initiation of an HBV immunization program.[19]

Between 10% and 25% of HCC cases are thought to be due to HCV infection.[20] Successful antiviral therapy may prove beneficial to decrease the risk of HCC in HCV-infected patients; however, this reduction has yet to be conclusively shown in a randomized clinical trial.

Heavy alcohol intake, defined as prolonged periods of consumption of more than 50–70 g/day, is understood to be an important risk factor for HCC. In addition, heavy alcohol intake has a synergistic effect with chronic HBV or HCV infection, perhaps by promoting liver damage and cirrhosis. In one study, heavy alcohol intake combined with concomitant HBV or HCV infection resulted in a twofold increase in the odds ratio for HCC risk compared with heavy alcohol intake alone.[21]

The mycotoxin aflatoxin, produced by the *Aspergillus* fungus, is recognized as a potent hepatocarcinogen. Dietary exposure to aflatoxin is an important risk factor in Asia and sub-Saharan Africa, where it commonly contaminates foods such as peanuts, grain, legumes, and corn. In a recent meta-analysis, the population-attributable risk of aflatoxin-related HCC was estimated to be 17%.[22] In areas of high exposure, reducing aflatoxin exposure to non-detectable levels may reduce HCC cases by approximately 23%. There is evidence that aflatoxin can act in concert with chronic HBV infection to further increase the risk of HCC. For example, aflatoxin exposure (measured by the urinary excretion of aflatoxin metabolites) alone was associated with a fourfold increase in HCC, and in the same study, HBV infection alone was associated with a sevenfold increase.[23] Among patients with both risk factors, the risk of HCC increased sixtyfold.

Nonalcoholic fatty liver disease (NAFLD), the hepatic consequence of obesity and diabetes, is a common form of chronic liver disease in developed countries. Its incidence is growing, following the patterns of rising rates of obesity and diabetes. Nonalcoholic steatohepatitis (NASH) is a severe

form of NAFLD and is thought to lead to HCC via progression of liver cirrhosis. In fact, NASH may account for a large proportion of idiopathic or cryptogenic cirrhosis.[24,25] NASH is associated with a histopathology showing features of steatosis, hepatocellular injury, and fibrosis.

Several other risk factors for HCC have been documented in the literature, including cigarette smoking, oral contraceptive use, hemochromatosis, and diet. The importance of genetics has been investigated, primarily to assess why only a small subset of patients with the established risk factors develop cirrhosis and progress to HCC. Because many of these studies are small and limited in scope, further research is needed to more fully define the role of genetics in HCC pathogenesis.

A population-based analysis of data from Medicare and the Surveillance Epidemiology and End Result (SEER) registry reported that in patients diagnosed with HCC during 1996–1999, the most common risk factors were alcohol-induced liver disease (22%) and HCV infection (21%).[26] In this study, nearly 40% of HCC cases were not associated with HCV, HBV, alcohol-induced liver disease, nonspecific cirrhosis, or nonspecific hepatitis. This finding suggests that other factors, such as diabetes, obesity, and NAFLD, might also be important contributors to HCC pathogenesis. Diabetes was found to be associated with a threefold increase in the risk of HCC among individuals with other risk factors (including HCV and HBV).[27] The association between diabetes and HCC was twofold among patients who lacked these risk factors.

Tumor Staging

Although tumor staging plays an essential role in guiding treatment decisions, it is important to consider that in HCC, patient prognosis is affected not only by the stage of the tumor at diagnosis but also by the degree to which underlying liver function is affected. A number of staging systems are available for use in HCC, and there is no worldwide consensus on a preferred system. According to guidelines from the American Association for the Study of Liver Disease (AASLD), staging systems for HCC should account for tumor stage, liver function, and physical status.[28] The impact of treatment should also be considered when estimating life expectancy. The only staging system currently in use that addresses each of these concerns is the Barcelona Clinic Liver Cancer (BCLC) classification, which was developed using data from several independent studies that included patients with different disease stages who received a range of treatment modalities.[29] The BCLC system relates staging to treatment modalities as well as an estimation of life expectancy. The major advantage of the BCLC system is that it can be used to identify those patients with early-stage HCC who may benefit from curative therapies, and differentiate them from patients with more intermediate-stage or advanced-stage disease who would benefit more from life-extending and palliative treatments. In contrast, the Child-Pugh classification system assesses only the severity of liver disease of cirrhotic patients. Five variables are factored into the final Child-Pugh score: 1) severity of ascites; 2) severity of encephalopathy; 3) abnormality in serum bilirubin levels; 4) abnormality in serum albumin levels; and 5) clotting times.[30] The model for end-stage liver disease (MELD) score is used to prioritize patients awaiting liver transplantation, and provides an estimate of the risk of death from liver disease within the next 3 months. Three laboratory values are considered when calculating the MELD score: 1) serum bilirubin levels; 2) the International Normalized Ratio (INR), a measure of the liver's ability to produce blood clotting factors; and 3) serum creatinine levels.[31] Both the Child-Pugh and MELD scores consider only liver function, and do not incorporate the patient's performance status or cancer-related symptoms, and thus cannot provide an accurate determination of the patient's prognosis or potential benefit from treatment.[32] Other staging systems that have been historically used in HCC patients include the tumor/node/metastasis (TNM) system, a standard oncology classification scheme that has limited prognostic utility in HCC patients, the Cancer of the Liver Italian Program (CLIP) system, and the Okuda system, which considers both tumor size and liver function but is unable to stratify patients with early-stage or intermediate-stage disease.[33,34]

In the BCLC system, patients with a performance status of 0 and Child-Pugh A disease are considered to have very early-stage disease, with a single tumor lesion of less than 2 cm. Patients with either Child-Pugh A or B disease who have a performance status of 0–2 are further classified into early-stage (stage A), intermediate-stage (stage B), or advanced-stage (stage C) disease. Patients with early-stage disease have at least 3 nodules (all <3 cm) and a performance status of 0. These patients have preserved liver function and are candidates for long-term potentially curative treatments, such as surgical resection, liver transplantation, and percutaneous ablation. Early-stage patients have a 5-year survival rate that ranges between 50% and 75%. Intermediate-stage patients have multinodular disease and a performance status of 0, with no cancer-related symptoms and no macrovascular invasion or extrahepatic spread. These patients are optimal candidates for treatment with hepatic artery catheter-based approaches such as transarterial chemoembolization (TACE). Patients with advanced-stage disease have evidence of portal invasion, evidence of lymph node involvement (N1) or metastatic disease (M1) on tumor staging, and a performance status of 1–2. Advanced-stage patients present with cancer-related symptoms and/or have vascular invasion or extrahepatic spread. Historically, their 1-year survival is only 50%, and

until the approval of sorafenib, there was no agent shown to improve survival. This is still an area of unmet need for patients who cannot tolerate sorafenib and for patients who progress while on sorafenib. Terminal-stage patients (stage D) have a performance status of 3–4 and Child-Pugh C disease, with extensive tumor involvement, severe deterioration of physical capacity, and/or major impairment of liver function. Terminal-stage, or end-stage, patients have a median survival of fewer than 3 months and receive only palliative care to control their symptoms.

In support of a growing movement towards the use of the BCLC system, Marrero and colleagues concluded that it provided the best prognostic stratification for a cohort of HCC patients when compared with 6 other staging systems.[35] In this comparison study, the BCLC system was found to have the best independent predictive power for survival. The recently updated revision to the American Association for the Study of Liver Diseases (AASLD) guidelines for management of HCC concludes that the BCLC staging system has become the de facto staging system in use, as it has come to be widely accepted in clinical practice and is also being used in many of the current prospective clinical trials of investigational HCC agents.[36]

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Strategies for Hepatocellular Carcinoma Surveillance and Diagnosis

Robert G. Gish, MD

In patients with HCC, it is important to be aware of the different goals of screening and surveillance.[1] Screening is an initial test performed on asymptomatic individuals to allow for early detection of a disease, thereby permitting therapeutic intervention and improved outcomes. As noted in the AASLD Practice Guidelines on the Management of Hepatocellular Carcinoma, surveillance is a test performed after screening, on a regular basis, and should be offered in settings in which screening tests and recall procedures have been standardized, and where quality control procedures have been established.[1] Overall, the goal of HCC surveillance is not only early detection, but also decreased disease mortality. Factors to consider include the level of risk needed to trigger surveillance, the surveillance tests that should be used and how frequently, and how abnormal results should be addressed.

Surveillance Techniques

Radiological and serological tests are both used for HCC surveillance (Figure 1). Importantly, imaging as a surveillance technique is used in the setting of advanced liver disease (most commonly cirrhosis) as well as in those patients at risk for HCC but without cirrhosis. Ultrasonography is the most frequently used radiological tool for HCC surveillance. During ultrasound, an HCC lesion may appear echogenic (due to the presence of fat in the cells) or hypoechoic, or it may have a "target lesion" appearance.[1] The use of ultrasound is limited by its dependence on the operator's skill, the wide quality of imaging studies, the time spent performing the test, and variable results, particularly in obese individuals.

Other radiological tools used to supplement ultrasound to make the diagnosis of HCC during ultrasound surveillance include computed tomography (CT) and magnetic resonance imaging (MRI). MRI and CT are not tools for standard surveillance, and are not deemed cost-effective. In practice, MRI and CT are used for patients who are not good candidates for US, such as those patients with a high body mass index. After a liver nodule is detected on ultrasound, MRI or CT are relied upon to make a radiological diagnosis. Most typically, an MRI scan is used due to the lack of radiation. If there is a contraindication to an MRI, or if the radiology expertise is CT-focused, then a 4-phase multidetector CT scan is used, which consists of a nonenhanced phase, an arterial phase, a portal vein phase, and a delayed phase.[2] Using MRI or 4-phase CT, HCC typically appears as a hyperattenuated lesion in the arterial phase, with a loss of enhancement (ie, rapid washout) in the portal venous and/or delayed phase. MRI is associated with a higher cost, but evidence supports that it provides greater sensitivity in HCC surveillance while avoiding exposure to ionizing radiation.[3] Gadolinium chelates are generally used to perform dynamic contrast-enhanced MRI, which reveals a typical HCC lesion to have a hyperintense signal intensity on T1-weighted images during the arterial phase and rapid washout during portal venous and delayed phases.[2] Newer targeted contrast agents have begun to emerge to enhance the sensitivity of MRI for HCC. These agents, including gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid and gadobenate dimeglumine, are taken up by normal liver cells but not by liver cancer cells, and thus are able to further enhance the diagnostic accuracy of standard confirmatory tests and can also be used as markers of hepatobiliary excretion.

Alpha-fetoprotein (AFP) is the most widely used and best-studied serological test for HCC surveillance. Persistently elevated AFP levels represent a risk marker for HCC development and can be used to define at-risk populations and supplement imaging tools. Most studies evaluating AFP levels have focused on their use in the diagnostic setting, where this test has the lowest utility. As a surveillance tool, AFP levels, alone, are inadequate. Other causes of AFP fluctuations include HBV or HCV infection flares and underlying liver disease or cirrhosis. AFP levels are now used to determine the need for alternate testing if an ultrasound test is negative while AFP levels are rising or remain elevated in the clinical setting. Additional serological markers that have been examined for their role in HCC surveillance include des-gamma-carboxy prothrombin (DCP), the lens culinaris agglutinin-reactive fraction of AFP (AFP-L3%), alpha-L-fucosidase, and glypican-3. In a clinical evaluation of AFP, DCP, and AFP-L13%, the sensitivity of each marker for the detection of HCC was 67.7%, 72.7%, and 61.6%, respectively.[4] When all 3 markers were combined, the sensitivity reached 85.9%. These serological markers have not been extensively studied in HCC surveillance, and therefore their use is not currently recommended as a primary tool.[1] Elevated AFP-L3% and DCP are correlated with a higher risk of vascular invasion found at pathology and postsurgical recurrence either with resection or with liver transplantation.

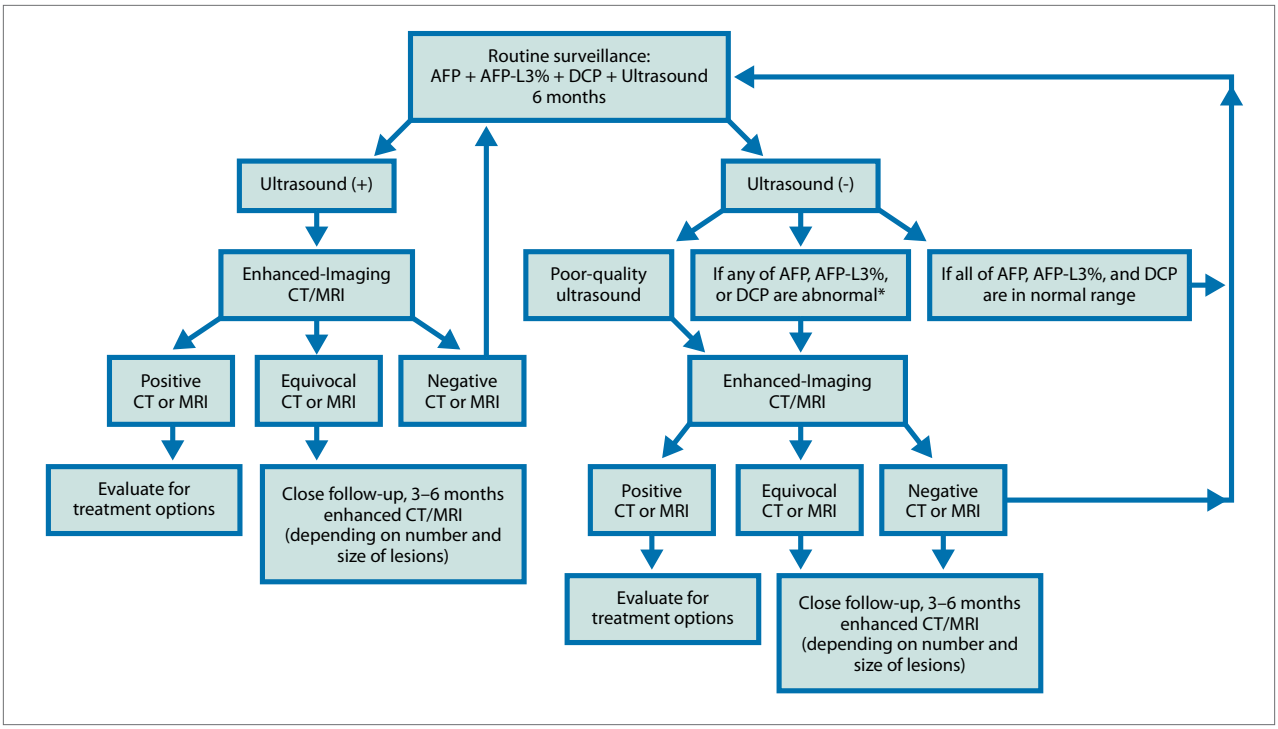

Figure 1. Hepatocellular carcinoma surveillance algorithm. *Positive AFP >20–200 ng/mL depending on the clinical scenario, AFP-L3% and DCP >upper limit of normal. AFP=alpha-fetoprotein; AFP-L3%=lens culinaris agglutinin-reactive fraction of AFP; CT=computed tomography; DCP=des-gamma-carboxy prothrombin; MRI=magnetic resonance imaging. Data based on Robert Gish, MD/Yuko Kono, MD, personal communication.

The sensitivity (true-positive rate) and specificity (true-negative rate) of several tests used for HCC surveillance were assessed in a systematic review of cross-sectional studies.[5] In 14 studies, ultrasound was demonstrated to have a sensitivity ranging from 30–100% (pooled estimate: 60.5%; 95% confidence interval [CI], 44–76%), and a sensitivity ranging from 73–100% (pooled estimate: 96.9%; 95% CI, 95–98%). The pooled positive and negative likelihood ratios for ultrasound were 17.7 and 0.5, respectively. As would be expected, the sensitivity and specificity of AFP testing, as assessed in 9 studies, differed according to the various cut-off ranges used in each of the studies. Overall, sensitivity decreased and specificity increased as the cut-off value increased. Spiral CT and MRI were also assessed as surveillance techniques. For spiral CT, the sensitivity ranged from 44–93% (pooled estimate: 67.5%; 95% CI, 55–80%), the specificity ranged from 56–100% (pooled estimate: 92.5%; 95% CI, 89–96%), and the pooled positive and negative likelihood ratios were 6.1 and 0.4, respectively. For MRI, the range of sensitivity was 54–100% (pooled estimate: 80.6%; 95% CI, 70–91%), the range of specificity was 57–100% (pooled estimate: 84.8%; 95% CI, 77–93%), and the pooled positive and negative likelihood ratios were 3.9 and 0.3, respectively.

Recently, a retrospective analysis of 638 patients with cirrhosis who underwent liver transplantation was performed to compare the abilities of CT, MRI, and ultrasound to detect HCC.[6] Of the 638 patients, 225 (35%) were confirmed to have HCC following pathological analysis of the liver explant. Infiltrative or extensively multifocal lesions were found to be present in 23 cases, leaving 202 cases evaluable for comparison. The overall lesion-based sensitivities for MRI (72%) were higher than for either ultrasound (46%) or CT (65%). For lesions less than 2 cm, ultrasound continued to be the least sensitive (21%) compared with either MRI (47%) or CT (40%). The sensitivity of ultrasound was increased when either CT or MRI imaging data were also available (*P*=.049). An earlier comparison of data from Snowberger and Sato showed similar results (Figure 2).[7,8]

Evidence Supporting HCC Surveillance

There has been a debate as to whether surveillance is effective in reducing mortality or is cost-effective in the management of HCC. The question of what constitutes a worthwhile intervention was addressed nearly 2 decades ago in a paper by Naimark and colleagues that quantitated a clinically significant gain as an improvement in survival of 3 months.[9] Further, surveillance can be considered cost-effective if it achieves this 3-month improvement in survival at a cost of less than $50,000 per life-year saved.[10] The clinical efficacy of surveillance must be determined

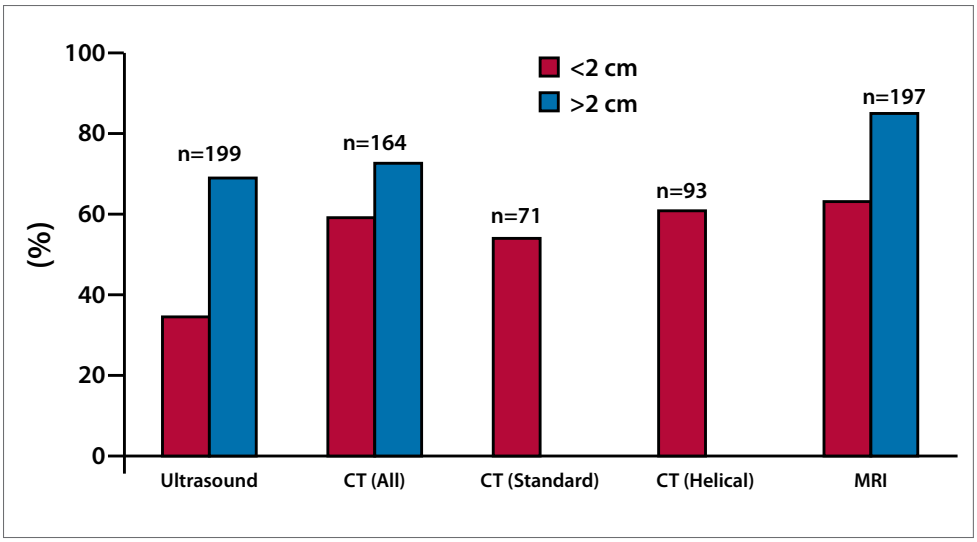

Figure 2. Comparison of the ability of CT, MRI, and ultrasound to detect hepatocellular carcinoma. CT=computed tomography; MRI=magnetic resonance imaging. Data from Snowberger N et al. *Aliment Pharmacol Ther.* 2007;26:1187-1194[7] and Sato T et al. *Hepatol Int.* 2009;3:544-550.[8]

through randomized controlled trials, but the cost efficacy can be estimated in modeling studies.

One of the first randomized controlled trials to establish a benefit in overall survival with HCC surveillance was performed in 18,816 Chinese patients with current or prior HBV infection (Figure 3).[11] Patients were randomized to either a surveillance arm (performed with an AFP test and ultrasound every 6 months) or a control nonsurveillance arm. Only 58.2% of the individuals enrolled in this study showed optimal adherence to surveillance techniques by completing the screening offered. However, among patients in the surveillance arm, the risk of HCC-related mortality was reduced by 37%. The total mortality rate was 83.2 deaths per 100,000 in the surveillance arm versus 131.5 deaths per 100,000 in the control arm. After a 5-year follow-up, the survival rate in the screening arm was significantly higher than in the control arm (P<.01). Although this large study has several limitations, including a narrow population of employed patients and probable lead-time bias, it is the first to demonstrate a benefit for HCC surveillance.

A retrospective analysis in the United States was performed in 269 patients with cirrhosis and HCC.[12] Patients were retrospectively categorized into 3 groups according to the quality of their surveillance prior to diagnosis: group 1 received the standard of care surveillance (defined as ultrasound or another abdominal imaging technique administered at least once per year); group 2 received substandard surveillance (defined as a lack of abdominal imaging within 1 year of the cancer diagnosis); and group 3 received an absence of surveillance in patients not recognized to be cirrhotic. HCC had been diagnosed in stage I or II in 70% of group 1 patients, compared with only 37% of patients in group 2 and 18% of patients in group 3 (P<.001 for each comparison). Thus, more patients in the standard-of-care surveillance group had been diagnosed during the earlier stages of the malignancy, when interventions have a greater chance of success. Accordingly, significantly more patients in group 1 were able to undergo liver transplantation (32%) compared with group 2 or group 3 (13% vs 7%; P<.001 for each comparison). A clear gradient emerged across the surveillance groups with regard to their survival outcomes, with patients in group 1 showing a significantly improved rate of 3-year overall survival from their cancer diagnosis (39%) compared with group 2 (27%; P<.05) or group 3 (12%; P<.05).

One study used a post-hoc approach to determine the effectiveness of surveillance for HCC in patients with liver cirrhosis.[13] In this study, 1,436 cirrhotic patients with HCC were grouped into 2 categories: the first included patients whose HCC had been detected with periodic surveillance, and the second consisted of patients whose HCC had been incidentally detected. Patients in the surveillance group had smaller tumors and earlier-stage disease, often without vascular invasion or metastases. These patients were also more readily able to receive curative treatment options such as surgical resection, radiofrequency ablation, and percutaneous ethanol injection. Importantly, patients in the surveillance group achieved a significantly improved rate of 3-year overall survival compared with patients in the non-surveillance group (59.1% vs 29.3%; P<.01).

A computer-based state transition model was used to assess the costs, clinical benefits, and cost effectiveness of 6 surveillance strategies in cirrhotic patients ages 50 years or older.[14] These strategies included 1) annual ultrasound, 2) semiannual ultrasound, 3) semiannual ultrasound combined with AFP testing, 4) annual CT, 5) semiannual CT, and 6) annual MRI. Each of these strategies was

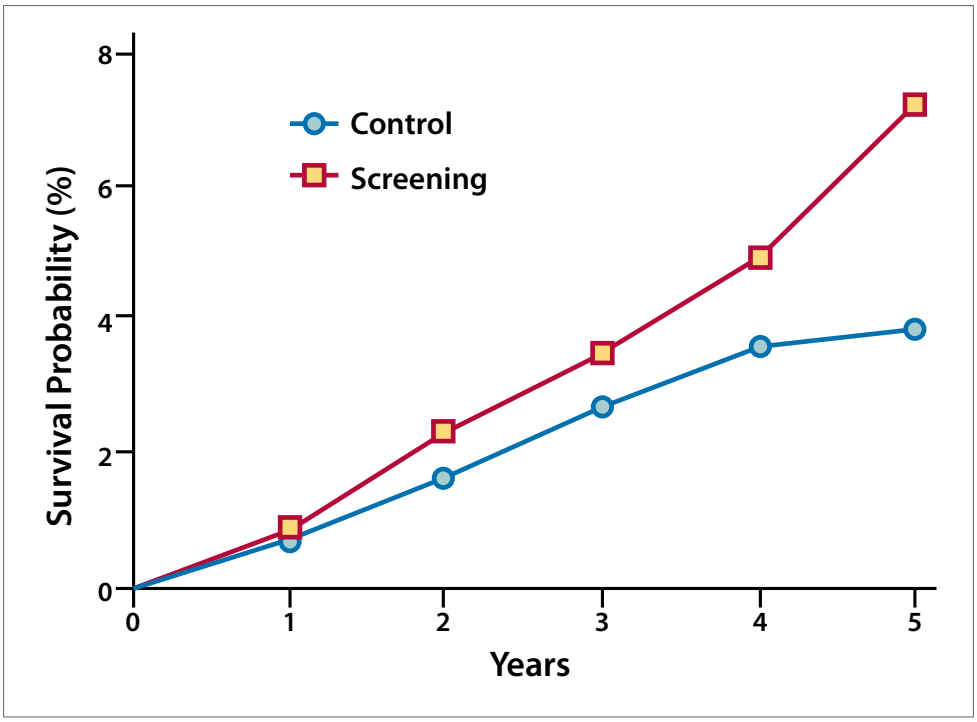

Figure 3. A study by Zhang and colleagues was one of the first randomized controlled trials to establish a benefit in overall survival when surveillance for hepatocellular carcinoma was performed in patients with current or prior hepatitis B virus infection. Adapted from Zhang BH et al. *J Cancer Res Clin Oncol*. 2004;130:417-422.[11]

compared with no surveillance. Semiannual ultrasound as a surveillance technique was found to increase the quality-adjusted life expectancy by an average of 8.6 months. This rate was increased to almost 3.5 years in patients with small treated tumors. These improved outcomes were found to come at a reasonable cost, with an incremental cost-effectiveness ratio of $30,700 per quality-adjusted life year. Semiannual CT, determined to be the most effective strategy with the greatest average increase in quality-adjusted life expectancy, had an incremental cost effectiveness ratio of $331,800. In comparison, annual MRI was more costly and less effective than both semiannual ultrasound and semiannual CT.

Surveillance Guidelines

Guidelines for surveillance and management of HCC are available from a variety of organizations. A unifying theme among the majority of these guidelines is that ultrasound is advocated as the chief surveillance strategy. There is a difference in opinion among these guidelines as to whether the ultrasound should be performed at 6-month or 12-month intervals, and if ultrasound should be combined with AFP testing as an adjunct part of the surveillance program (Table 1). The inclusion of AFP is chiefly a recognition that imaging techniques such as ultrasound are affected by operator training and error, and therefore these imaging data may often be substandard in many parts of the world.

In the AASLD guidelines, ultrasonography is the tool recommended for HCC surveillance; AFP alone should not be relied upon in this setting.[1] The guidelines further recommend that ultrasound surveillance be conducted at 6-month intervals, and they note that this interval need not be shortened in patients at high risk of developing HCC.

The updated AASLD guidelines state that there is no experimental evidence to indicate which level of risk should trigger surveillance.[1] However, these guidelines recommend that patients at high risk of developing HCC should be entered into surveillance programs. Several patient groups have been identified as exceeding the threshold incidence for the efficacy of surveillance (>0.25 life-years gained), including Asian male HBV carriers older than 40 years, Asian female HBV carriers older than 50 years, HBV carriers with a family history of HCC, African and North American blacks with hepatitis B at any age, any HBV patient with cirrhosis, patients with HBV/HCV-related cirrhosis, patients with stage 4 primary biliary cirrhosis, patients with genetic hemochromatosis and cirrhosis, patients with alpha 1-antitrypsin deficiency and cirrhosis, and "other" cirrhotic patients, defined in this article as patients who have fatty liver with cirrhosis. The benefit of surveillance remains uncertain in patients who are HBV carriers younger than 40

Table 1. Surveillance Guidelines for High-Risk Patients

Society or Institution	Guidelines
American Association for the Study of Liver Diseases (AASLD)[20,22]	Ultrasound every 6 months
European Association for the Study of the Liver (EASL)[23]	Ultrasound every 6 months
Asian-Pacific Association for the Study of the Liver (APASL)[24]	AFP + ultrasound every 6 months
National Comprehensive Cancer Network (NCCN)[25]	AFP + ultrasound every 6–12 months
United States Department of Veterans Affairs (VA)[26]	AFP + ultrasound every 6–12 months

years (for men) or younger than 50 years (for women) who do not have cirrhosis, patients with hepatitis C and stage 3 fibrosis, and patients with non-cirrhotic NAFLD. Further, recommendations regarding patients on the liver transplant waiting list state that HCC surveillance should be provided for these individuals as well. The reasoning for this inclusion is twofold: first, the development of HCC increases the patient's priority on the waiting list; and second, if left unchecked, HCC could develop and progress to a stage that would prompt removal of the patient from the waiting list.

Standard of care regarding HCC surveillance is to have different thresholds for surveillance in different disease states. Recommendations in HCC guidelines do guide provider behavior to a certain extent, but there are cases in which standard of care supersedes the recommendations in these guidelines and where AFP remains a mainstay of HCC surveillance in the community. In the community setting, guidelines can influence the standard of care, and physicians should be aware of the published data supporting a particular strategy.

A questionnaire sent to physician members of the AASLD elicited 554 responses, of which 473 were considered eligible for analysis.[15] Routine HCC screening of cirrhotic patients was reported in 84% of respondents; nearly half of these limited screening to patients with high-risk etiologies such as HBV or HCV infection. Both AFP testing and ultrasound were used for HCC screening by 69% of the respondents, further supporting the standard of care statement mentioned above.

Unfortunately, a recently published study suggested that poor HCC surveillance is more widespread than previously believed.[16] In this report, investigators assessed HCC surveillance data from 1,005 patients with chronic HCV infection who had cirrhosis or advanced fibrosis. All of the patients had been enrolled in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) trial. Both consistent surveillance (defined as ultrasound and AFP assessment performed at least once every 12 months) and surveillance failures (defined as an absence of screening, follow-up, or detection) were recorded. After a mean follow-up of 6.1 years, consistent surveillance was documented in 692 (68.9%) patients. However, 7.5% of patients failed to undergo HCC screening; almost all of these cases (94.1%) were attributed to lack of ultrasound. In a multivariate analysis adjusted for patient characteristics, the study site was the factor most strongly predictive of consistent surveillance (P<.001). After adjusting for study site, patient-related factors found to be independent predictors of consistent surveillance included complete adherence to clinic visits (hazard ratio [HR], 1.72; 95% CI, 1.11–2.63) and a platelet count exceeding 150,000 cells/mm^3 (HR, 1.28; 95% CI, 1.05–1.56). A total of 83 cases of HCC were identified. Of the 23 cases detected at late stage, 16 were due to absence of detection, 4 were due to lack of follow-up, and 3 were due to lack of screening.

Other studies also suggest that HCC surveillance is underperformed. For example, a retrospective, population-based analysis of a United States cohort of HCC patients older than 65 who had previously been diagnosed with cirrhosis was conducted with data from the SEER-Medicare databases.[17] Of the 1,873 patients included in the analysis, only 17% had received regular surveillance testing in the 3 years prior to their HCC diagnosis, and 38% had received inconsistent surveillance. Among those who received regular surveillance testing, only half (52%) underwent both AFP testing and ultrasound, whereas the rest underwent either AFP testing (46%) or ultrasound (2%). Patients who received regular surveillance were more likely to live in urban areas, have higher incomes, and be seen by a doctor with an academic affiliation.

In a similar but separate analysis of 3,903 HCC patients identified from SEER-Medicare databases, routine screening was reported in only 7% of cases.[18] Most of these patients (90%) received both AFP testing and ultrasound, but 9% received AFP testing only and 1% received ultrasound only. Factors found to be significantly associated with routine screening included younger age, female sex, Asian ethnicity, greater liver disease severity, and underlying cirrhosis or HCV and/or HBV infection in the absence of cirrhosis (P<.01 for all). Routine screening was more likely to occur in patients who were seen by a gastroenterologist compared with a primary care physician (odds ratio: 2.9; 95% CI, 1.83–4.64; P<.01), as well as for patients who were seen by physicians in hospital or academic settings (odds ratio, 1.77, 95% CI, 1.28–1.45; P=.01) or solo practice (odds ratio, 1.90; 95% CI, 1.44–2.50; P<.01) versus group practice.

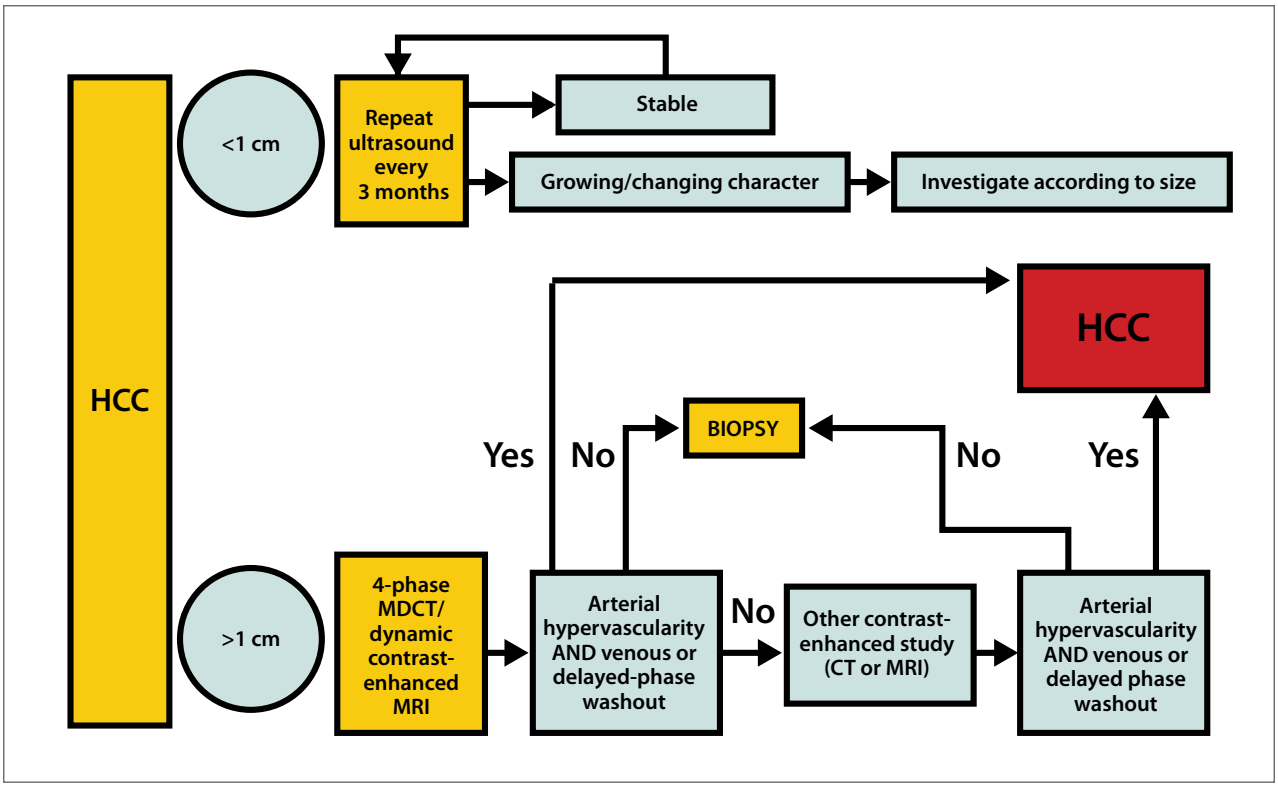

Figure 4. The diagnostic algorithm from the AASLD for HCC in patients who have hepatic nodules detected upon ultrasound surveillance. AASLD=American Association for the Study of Liver Diseases; CT=computed tomography; HCC=hepatocellular carcinoma; MDCT=multidetector row computed tomography; MRI=magnetic resonance imaging. Adapted from Bruix J, Sherman M. *Hepatology*. 2011;53:1020-1022.[20]

In a large, retrospective analysis of 13,002 HCV-infected United States veterans with cirrhosis, 42% had received 1 or more HCC surveillance tests within the first year of their cirrhosis diagnosis.[19] However, this percentage declined over subsequent years, with routine surveillance occurring in only 12% of patients after 2 years of follow-up.

Diagnostic Algorithm

The most recent update to the AASLD practice guidelines on the management of HCC included an updated diagnostic algorithm for HCC in patients who have hepatic nodules detected upon ultrasound surveillance.[20] Liver nodules that are less than 1 cm in diameter are not likely to be HCC. According to the diagnostic algorithm, these lesions should be followed with repeat ultrasound imaging every 3 months (Figure 4). If these small lesions show no evidence of growth suggestive of malignant transformation over a monitoring period of 1–2 years, they are determined to have a low likelihood of being HCC, and the patient can be returned to routine surveillance. In contrast, enlargement of these lesions over the follow-up period is suggestive of HCC and warrants further investigation. Liver nodules that are greater than 1 cm in diameter should undergo further evaluation with either 4-phase CT or dynamic contrast-enhanced MRI. If these further imaging studies reveal features typical of HCC (such as arterial hypervascularity and venous or delayed-phase washout), the lesion is then diagnosed and managed as HCC. However, if these features are not evident, a second contrast-enhanced study (either CT or MRI) is performed. If this second study reveals arterial hypervascularity and venous or delayed phase washout, a diagnosis of HCC is made. If not, image-guided core biopsy is considered. In this event, the guidelines strongly encourage expert pathology review because the differentiation between high-grade dysplastic nodules and HCC lesions can be challenging.[20] Pathologic examination of biopsy stains should include staining for glypican-3, heat shock protein 70, and glutamine synthetase; positivity for 2 of these 3 markers confirms HCC.[21] In the event of a negative biopsy, imaging studies should be conducted at intervals of 3–6 months until the nodule either disappears, enlarges, or displays diagnostic characteristics of HCC.[1] Enlargement of a lesion determined to be atypical for HCC should prompt a repeat biopsy.

This update specifically states that diagnosis of HCC should be based upon imaging techniques and/or biopsy.[20] However, HCC can be diagnosed radiologically without the need for biopsy if typical features are evident upon

imaging.[1] In the absence of advanced liver disease or cirrhosis, the imaging criteria must be reviewed in greater detail with a much lower threshold to perform biopsy. Some form of imaging, such as CT or MRI, is also required to determine the extent of the disease. The updated guidelines also recommend that AFP no longer be used in the diagnosis of HCC, primarily because this marker can also be elevated in either intrahepatic cholangiocarcinoma or some colon cancer metastases.

Since its original publication in the 2005 guidelines, the diagnostic algorithm has been validated, and the diagnostic accuracy of a single dynamic technique showing intense arterial uptake followed by contrast washout has been demonstrated. Because contrast-enhanced ultrasound may lead to a false-positive HCC diagnosis in patients with cholangiocarcinoma, this technique is not recommended.

Acknowledgment

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Current Treatment Approaches in HCC

Jorge A. Marrero, MD, MS

Historically, the treatment of HCC was complicated by the fact that the disease was diagnosed at an advanced stage, when the presence of cancer symptoms and liver function impairment limited treatment options. In contrast, current efforts to follow surveillance strategies in patients at high risk of developing HCC have led to the diagnosis of the disease at much earlier stages, when the patients have a much higher chance of benefiting from curative or potentially long-term therapies. Several therapeutic modalities are available for the treatment of HCC, and the choice of treatment is dependent upon the stage of HCC, the degree of underlying liver function, the presence of other comorbidities, the availability of a particular treatment, and the expertise and experience of the local clinical staff.

Surgical Resection

Surgical resection is the best treatment option for the small number of patients with single nodules, excellent liver function, and no underlying cirrhosis. In contrast, even if patients with underlying cirrhosis may initially benefit from resection, they have an increased risk for post-resection hepatic decompensation. Thus, patients with BCLC stage 0 disease are considered the optimal candidates for surgical resection. These patients have a performance status of 0, are Child-Pugh class A, and have normal portal pressure and bilirubin levels; they therefore have a minimal risk of post-resection hepatic decompensation. In fact, studies have demonstrated that normal bilirubin levels and the absence of clinically significant portal hypertension are the best predictors of excellent outcomes following resection, and patients with these characteristics have a 5-year survival exceeding 70%. In many centers, indication for surgery is limited to patients with a single tumor that is accessible for resection, as shown by imaging studies. However, the size of the lesion is generally not a clear-cut limiting factor, as some large tumors may not necessarily show evidence of invasion.

Measurement of portal pressure is considered to be a key step in determining whether patients should be considered candidates for surgery. Portal hypertension, developed as a consequence of cirrhosis, can be assessed using a platelet count of less than 100,000 cells/mm^3 in association with splenomegaly as a surrogate marker. The utility of portal hypertension as a measurement to help predict the outcome of patients following surgery and to help define optimal candidates for resection was confirmed in a retrospective review performed in 434 Japanese Child-Pugh class A patients.[1] The 5-year overall survival rate was 58% for those patients with portal hypertension prior to surgery (defined either by the presence of esophageal varices or a platelet count <100,000 cells/mm^3 in association with splenomegaly). This rate was significantly lower than the 71% rate of 5-year overall survival experienced by patients with no portal hypertension (P=.008).

Although surgical resection is considered to be potentially curative, the majority of patients eventually develop recurrence. After 5 years, the recurrence rate exceeds 70%.[2,3] The most critical factors to consider for predicting recurrence in surgical patients are the presence of microvascular invasion and the presence of additional tumor sites beyond the primary lesion.[4] Recurrence resulting from dissemination of the primary tumor typically occurs within the first 3 years following surgery. No adjuvant therapies have yet proven effective to help prevent recurrence following resection. However, the ongoing STORM (Sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma) trial is evaluating the use of sorafenib as adjuvant therapy in HCC patients, and these results are eagerly awaited.[5]

Local Ablation Treatments

In cases where surgical resection and liver transplantation are not possible, locoregional treatments are the best treatment option. These treatments involve tumor cell destruction either through the injection of chemical substances (such as ethanol, acetic acid, or boiling saline) or by modifying the temperature in the tumor (through application of radiofrequency, microwave, laser treatment, or cryotherapy). According to the AASLD guidelines, radiofrequency ablation (RFA) is the treatment of choice for local ablation, but percutaneous alcohol injection (PEI) is also considered to be an important therapeutic tool.[4] The primary limiting factor for ablation is the location of the tumor. Instances where the tumor is located particularly close to the gallbladder or lungs may preclude the use of an ablative technique.

PEI involves the coagulation necrosis of tumors via cellular dehydration. It is most effective in tumors larger than 2 cm (with a tumor cell necrosis rate of 90–100%), and gradually diminishes in efficacy as the size of the tumor increases (with tumor cell necrosis rates of 70% and 50% in

tumors 2–3 cm and 3–5 cm, respectively).[6-8] Although PEI is relatively inexpensive and has a low rate of adverse events, it is associated with a high rate of recurrence. Further, most patients require repeated injections on different days to ensure that the ethanol is able to access the entire tumor.[9]

RFA results in a much wider region of tumor necrosis through the application of electrodes that deliver heat directly to the tumor. In comparison to PEI, RFA results in a similar rate of tumor cell necrosis for tumors smaller than 2 cm, but requires fewer treatment applications.[10,11] The efficacy of RFA is improved over PEI in tumors larger than 2 cm.[10-12] A systematic review of randomized trials demonstrated that RFA was associated with significant improvement compared with PEI in the rate of 3-year overall survival (odds ratio, 0.477, 95% CI, 0.34–0.67; $P<.001$).[12] Like PEI, RFA is also associated with a significant risk of recurrence that is comparable to surgical resection.

Recently, results of the phase III HEAT (Hepatocellular Carcinoma Study of RFA and ThermoDox) trial were reported.[13] This study was an international, multicenter, randomized, placebo-controlled, phase III trial that randomized 701 patients with unresectable HCC (tumor sizes 3–7 cm) to treatment with either RFA plus an investigational heat-activated formulation of liposomal doxorubicin or RFA alone. The results were negative, in that the combination of the novel doxorubicin formulation with RFA did not meet the primary endpoint of demonstrating a 33% improvement in progression-free survival with 80% power ($P=.05$) compared with RFA alone.

The AASLD guidelines recommend that these local ablation treatments are a safe and effective therapy for patients who are unable to undergo surgical resection or as a bridge to liver transplantation.[4] Further, the AASLD guidelines also conclude that for HCC tumors exceeding 2 cm, RFA is associated with a more reliable necrotic effect in the tumor and results in better efficacy.

Liver Transplantation

Liver transplantation is another potentially curative option for HCC patients, and it is the best treatment option for patients with decompensated cirrhosis. Liver transplantation is most likely the best treatment option for HCC because it removes not only the tumor but also the diseased organ. However, due to the ever-present shortage of available organs, only those patients with early HCC who have the highest likelihood of survival after transplant are placed on the liver transplantation waiting list.

A seminal study by Mazzaferro and colleagues established the Milan criteria for HCC, which defined the tumor burden that could best be treated with liver transplantation.[14] In this study, patients with 1 lesion that was no larger than 5 cm or up to 3 lesions each 3 cm or smaller in diameter had a 5-year overall survival rate of 75% and a tumor recurrence rate of less than 15%. This tumor burden is compatible with early-stage HCC in the BCLC staging system.

Priority for assignment to the liver transplantation waiting list is based upon the MELD score, which was designed as a clinical tool to predict early mortality in chronic liver disease of viral or alcoholic origin.[15] However, MELD is not able to predict mortality in HCC, and therefore a "MELD exception" has been developed to assign extra points to HCC patients on the basis of the size of their tumor burden.[16,17] This exception has resulted in an increased number of liver transplantations being performed in HCC patients, but the overall effect on survival has not been determined. Future criteria have been proposed that would additionally incorporate a 3-month waiting period as a means to screen out patients with rapidly progressing tumors.[4,18]

Transarterial Chemoembolization

For patients with intermediate-stage HCC according to the BCLC system, transarterial chemoembolization (TACE) is a standard of care. HCCs are characteristically highly vascular and depend on this blood flow for the delivery of nutrients and oxygen to the tumor center. By temporarily blocking the arterial blood flow, TACE is able to abolish the primary blood supply to HCC tumors while the liver itself remains perfused with blood from the portal vein. The technique involves administration of a chemotherapeutic drug (most commonly doxorubicin or cisplatin), followed by an occluding agent, directly into the artery through a catheter. TACE results in extensive tumor necrosis in more than half of patients. Unfortunately, TACE is not considered curative and results in only a modest improvement in survival.

TACE techniques have historically been highly variable according to the center where they were performed. However, the introduction of doxorubicin-loaded drug-eluting beads (DEB-TACE) has standardized the technique. These drugs ensure a higher and more predictable intratumoral delivery of the cytotoxic agent. DEB-TACE was compared with conventional lipiodol-based TACE in the randomized phase II PRECISION V trial.[19] DEB-TACE was associated with improved outcomes, including complete response (27% vs 22%), objective response (52% vs 44%), and disease control (63% vs 52%); however, the hypothesis of superiority was not statistically met. Statistically significant improvements in objective response were noted when patient analysis was limited to those individuals with Child-Pugh class B disease, a performance status of 1, bilobar disease, and recurrent disease. Importantly, patients randomized to DEB-TACE showed a significantly lower incidence of both serious liver toxicity ($P<.001$) and doxorubicin-related adverse events ($P=.0001$).

In randomized trials, TACE has resulted in modest but significant increases in survival over symptomatic supportive

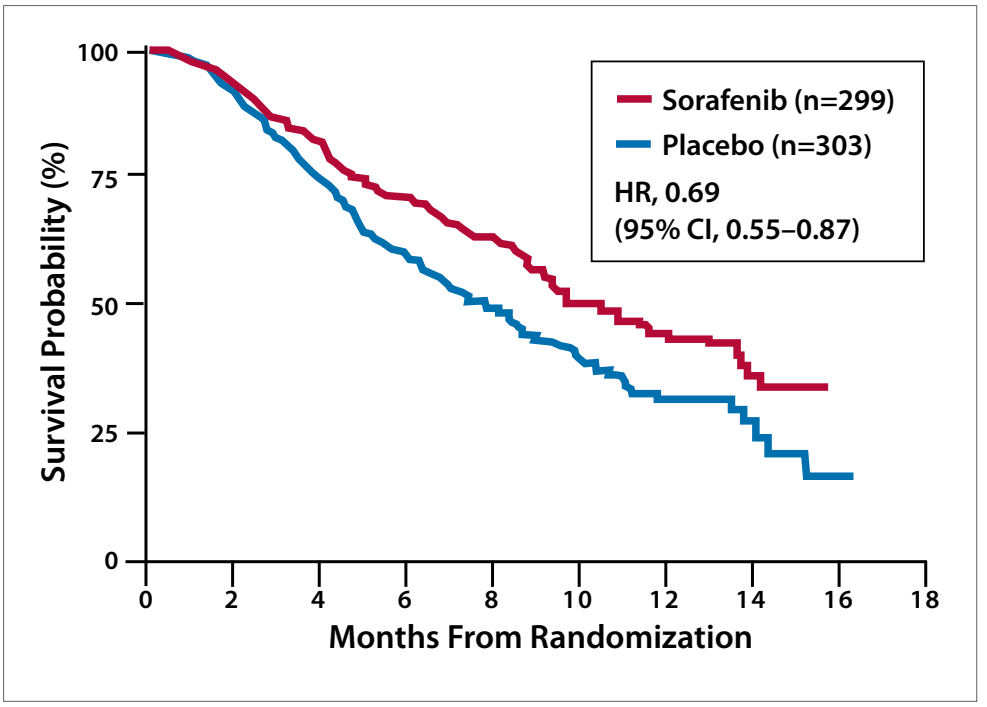

Figure 1. In the SHARP study, 602 patients with advanced hepatocellular carcinoma were randomized to treatment with either sorafenib or placebo. At an interim analysis, the trial was stopped after it became evident that there was a significant survival advantage associated with sorafenib. CI=confidence interval; HR=hazard ratio; SHARP=Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol. Adapted from Llovet JM et al. *N Engl J Med*. 2008;359:378-390.[23]

care. In a study of patients with HCV-related cirrhosis and unresectable multifocal HCC, the 1-year and 2-year survival rates were 82% and 63%, respectively, for patients undergoing TACE compared with 63% and 27% for controls.[20] HBV patients with unresectable multifocal HCC also demonstrated a significant survival benefit with TACE compared with controls at 1 year (57% vs 32%), 2 years (31% vs 11%), and 3 years (26% vs 3%).[21] In a subsequent meta-analysis, it was concluded that TACE resulted in an increase in the 3-year survival rate from 10% to 40–50%, and an accompanying increase in median survival from 16 to 20 months.[22]

Targeted Therapies: Past, Present, and Future

The field of targeted and systemic therapy for HCC is an area of very robust activity, with numerous clinical trials. Importantly, the only positive phase III randomized clinical trials have been with sorafenib versus placebo. The multikinase inhibitor sorafenib is the best and currently the only treatment option approved for patients with advanced-stage HCC. Sorafenib was established as the standard of care for these patients following the SHARP (Sorafenib Hepatocellular Carcinoma Assessment Randomised Protocol) trial, a large, randomized, placebo-controlled, phase III study. In the SHARP study, 602 advanced HCC patients were randomized to treatment with either sorafenib or placebo.[23] At an interim analysis, the trial was stopped after it became evident that there was a significant survival advantage associated with sorafenib (hazard ratio: 0.69; 95% CI, 0.55–0.86; *P*=.0005; Figure 1). The median overall survival in the sorafenib arm was 10.7 months compared with 7.9 months in the placebo arm. Additionally, the median time to progression was significantly prolonged among sorafenib-treated patients (5.5 vs 2.8 months). These results were subsequently recapitulated in the Asia-Pacific study, but notably in a cohort of patients with a different natural history of disease.[24] In clinical use, sorafenib has been associated with a number of adverse events, some of which may cause premature discontinuation due to intolerability.

Since sorafenib has been established as the first-line therapy for patients with advanced-stage HCC, numerous studies have since compared it to novel targeted agents, such as sunitinib, linifanib, and brivanib. None of these agents have demonstrated superiority to sorafenib. Another approach is to increase the efficacy of sorafenib alone by combining it with another agent. The phase III SEARCH (Sorafenib and Erlotinib, a Randomized Trial Protocol for the Treatment of Patients With Hepatocellular Carcinoma) trial failed to show a benefit for sorafenib plus erlotinib over sorafenib alone.[25] The combination strategy will again be tested in the Cancer and Leukemia Group B (CALGB) 80802 trial, which will compare sorafenib plus doxorubicin versus sorafenib alone.[26]

An area of critical unmet need in which targeted therapies are being applied is progression following sorafenib. In a randomized, placebo-controlled phase II trial of patients with advanced HCC and Child-Pugh A cirrhosis who had progressed on or were unable to tolerate sorafenib, the selective oral inhibitor of the MET tivantinib was found to prolong time to progression compared with placebo (1.6 vs 1.4 months, hazard ratio, 0.64; 95% CI, 0.43–0.94; *P*=.04).[27] Ramucirumab, a monoclonal antibody directed against the VEGF receptor 2, is currently under evaluation in the REACH phase III trial as second-line treatment for patients who have failed sorafenib. Other agents under active clinical investigation in this setting include everolimus, mapatumumab, and brivanib.

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Extending Survival With the Use of Targeted Therapy for the Treatment of Hepatocellular Carcinoma: Discussion

Robert G. Gish, MD
Richard S. Finn, MD

Robert G. Gish, MD Staging is a critical component in the overall discussion of HCC. There have been a number of different staging systems used in the past. Why did so many of these—namely, the Okuda system, the TNM system, and the CLIP score—fade from widespread use?

Richard S. Finn, MD This question addresses the goals of staging in HCC. In clinical practice, staging helps determine prognosis and also provides evidence-based direction as to which treatment strategies should be implemented. The challenge with TNM is that it ignores a large competing risk for prognosis, which is the underlying liver disease. TNM serves very well for a patient who has a resection. However, staging with TNM is difficult because many of its determinants require some pathological knowledge, and most patients lack a biopsy specimen at diagnosis.

The other systems are not completely obsolete. We are trying to develop a common language in clinical research. That is an important factor, because right now, the only positive randomized data for a systemic therapeutic agent in liver cancer are for sorafenib, from the SHARP study and the Asia Pacific study.[1,2] Both of these studies used the BCLC paradigm for assessing and randomizing patients. As we move forward, I think these data will be a benchmark against which new interventions will be compared. With that stated, I suspect that the other staging systems are often utilized in practice.

Robert G. Gish, MD Should hepatologists and surgeons assess the ECOG performance status of every HCC patient?

Richard S. Finn, MD This is an important point because performance status is one of the main factors used to stratify patients within the BCLC staging system. We know that, in general, an oncology performance status is considered to be an independent prognostic factor. In general, patients who are accrued to clinical studies must have a higher performance status, because as the performance status of a patient decreases, his or her odds of benefitting from a given intervention also become reduced, and the overall prognosis deteriorates.

In the context of HCC specifically, within the framework of the BCLC system, performance status was found to be an independent prognostic factor for outcome, which is the primary reason why it became incorporated into the staging system. It is an especially important point for distinguishing intermediate- and advanced-stage HCC. It is, however, an area of interest and some debate, because according to the BCLC criteria, patients with liver-confined disease who have symptoms and are being affected by their disease tend to benefit more from systemic treatment than from chemoembolization. In practice, many physicians and centers do not necessarily use performance status as a discriminator between BCLC stage B and stage C. There is still much to be learned regarding the importance of that distinction.

Robert G. Gish, MD Does the RECIST criteria, which is now being used in many of the prospective clinical trials currently under way, have a role in clinical practice?

Richard S. Finn, MD This question addresses the point of assessing the effect of an intervention in HCC, which is again an issue affecting both research and practice. The RECIST criteria were put forward to assess response to a given intervention in prospective oncology studies, and are calculated by measuring the sum of the longest diameters of a tumor. With regard to radiographic progression, according to the RECIST criteria, an increase of 20% or more from baseline or nadir in tumor size is considered progression, and a decrease of 30% or more is considered a partial response. Complete resolution of all measurable tumors would be considered a complete response. Patients who do not meet any of these criteria are considered to have stable disease. In the context of HCC, given the unique imaging characteristics of these lesions within the liver, it is possible that as we assess new interventions, the degree of vascularity should also be considered in addition to RECIST criteria. This is especially relevant in an intervention such as TACE, which can often devascularize a tumor but does not necessarily

result in tumor shrinkage. However, if the hypervascularity is removed, this might be considered a significant biologic affect, and one that is not captured in RECIST. Recently, the term *modified RECIST* (mRECIST) has been coined, which takes into account not only the total size of the tumor, but also the longest diameter of the hypervascular tumor.

We know in oncology that response rate alone does not necessarily translate into a survival advantage. Thus, there has long been an interest in using surrogate measures for survival, especially in diseases that might have a long natural history. For example, progression-free survival is measured as the time on-study before a patient experiences tumor progression by RECIST criteria (or before the patient withdraws from the study due to toxicity, death, or another reason). Another surrogate is time to progression, a pure radiographic endpoint that ignores other causes of progression. However, neither progression-free survival nor time to progression have a validated correlation to survival in HCC. This is an especially important point, because some of the examples of recent failures in targeted agents have been of drugs that have produced a higher response rate by RECIST as well as an improvement in time to progression compared with sorafenib, but did not result in improved survival. In a recent phase III second-line study, brivanib showed better activity than placebo in all measurements except overall survival.[3,4]

We are still trying to determine the best way to assess activity of a given intervention in HCC. It is important to note that in the SHARP study, patients were not required to stop sorafenib when they showed evidence of radiographic progression by RECIST. As long as they were tolerating the drug, and the physician believed they were getting some clinical benefit, they were allowed to continue treatment until clinical progression. Clinical progression would reflect a decrease in performance status, progression in liver dysfunction, or a similar occurrence. This idea is interesting, especially for a drug that is generally cytostatic.

Robert G. Gish, MD Notably, in the package insert for sorafenib, the indication includes discontinuation with clinical or symptomatic progression, and not just radiographic progression. This is a very important point missed by many hepatologists.

There have now been studies that suggest there is no difference between bead embolization and chemoembolization as a bridge to transplant. What would be your explanation for such an observation?

Richard S. Finn, MD First, it is important to remember that the randomized data supporting the use of chemoembolization in the management of HCC is not very robust. Multiple studies comparing chemoembolization with best supportive care or bead embolization have shown that chemoembolization is associated with improvements in benefit. The point is that all of these studies have been performed in highly selected patient populations. Clearly, in clinical practice, we have expanded the use of chemoembolization to patients who would not necessarily participate in these studies.

Many physicians do not consider HCC to be a particularly chemosensitive tumor. Thus, the idea behind chemoembolization is that very high concentrations of chemotherapy are injected directly into the tumor bed. I think many of us also suspect that just the embolization component, in which the tumor is starved of its blood supply, plays a significant role in the anti-tumor activity. I do not foresee that physicians will stop using chemoembolization based on these reports. There is still a need for strong data to determine the right treatment approach.

In regards to the pretransplant setting, the take-home point is that many physicians offer TACE or RFA to HCC patients on the transplant waiting list, not because we think it alters the course of their disease, but because it helps to keep their imaging studies in check so that they can continue to qualify for a transplant. There are no definitive data supporting the use of RFA or TACE to improve a patient's post-transplant outcome. It is just a matter of bridging them to transplant to keep them within the Milan size criteria.

Robert G. Gish, MD Likely each of these interventions may both have equal abilities to keep the tumor growth down.

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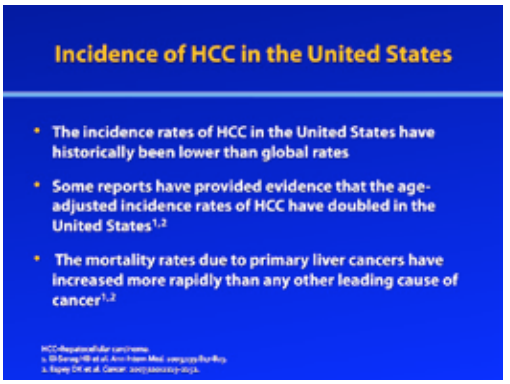

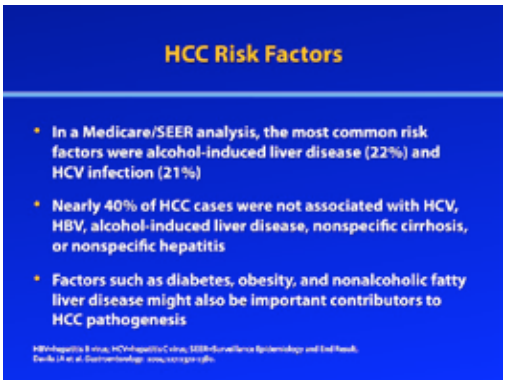

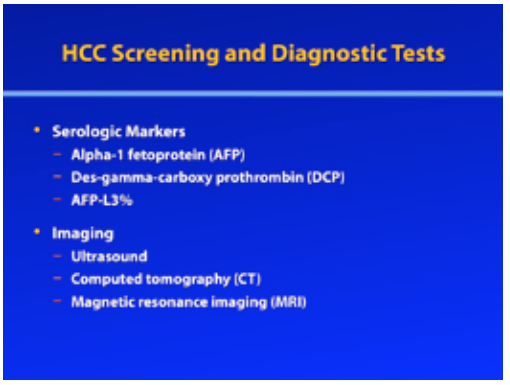

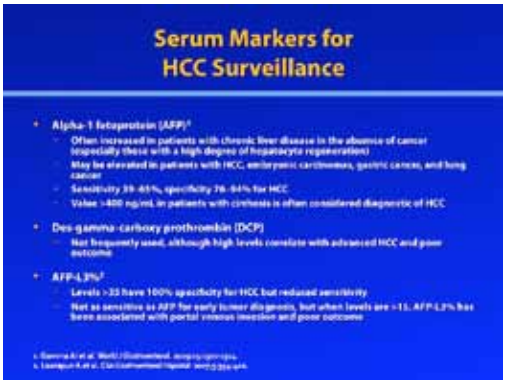

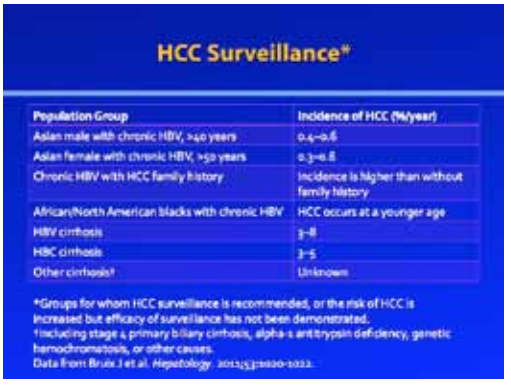

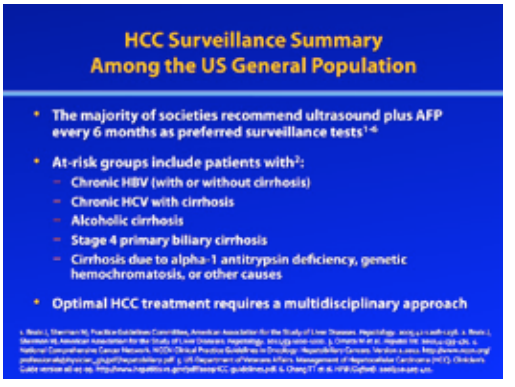

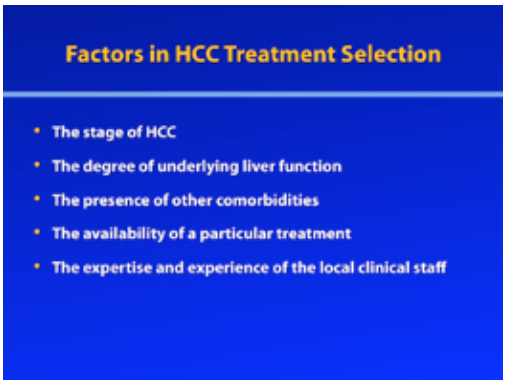

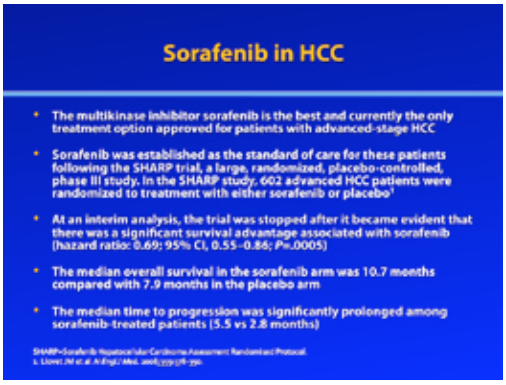

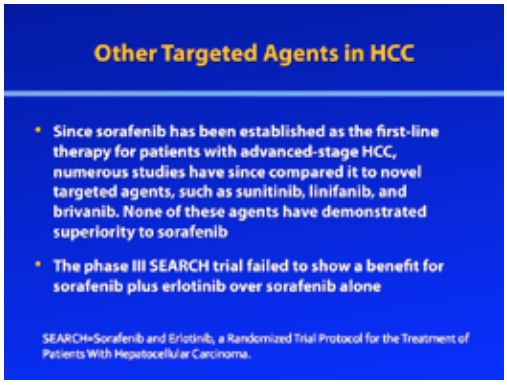

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Extending Survival With the Use of Targeted Therapy in the Treatment of Hepatocellular Carcinoma

CME Post-Test: *Circle the correct answer for each question below.*

1. Liver cancer is the ___ cause of cancer-related deaths worldwide.

   a. Leading
   b. Second-leading
   c. Third-leading
   d. Fourth-leading

2. Estimates suggest that hepatocellular carcinoma (HCC) accounts for up to ___ of primary liver cancers.

   a. 75%
   b. 80%
   c. 85%
   d. 90%

3. Approximately how many HCC cases are thought to be due to infection with hepatitis C virus?

   a. 10–25%
   b. 30–40%
   c. 45–60%
   d. 65–75%

4. Which radiological tool is used most often in HCC surveillance?

   a. Computed tomography
   b. Magnetic resonance imaging
   c. Radiography
   d. Ultrasonography

5. Which serological test is the most widely used and best-studied in HCC surveillance?

   a. Alpha-fetoprotein
   b. Alpha-L-fucosidase
   c. Des-gamma-carboxy prothrombin
   d. Glypican-3

6. Which treatment option is best for HCC patients with single nodules, excellent liver function, and no underlying cirrhosis?

   a. Percutaneous alcohol injection
   b. Radiofrequency ablation
   c. Surgical resection
   d. Transarterial chemoembolization

7. What treatment is the standard of care for patients with intermediate-stage HCC according to the Barcelona Clinic Liver Cancer (BCLC) system?

   a. Percutaneous alcohol injection
   b. Radiofrequency ablation
   c. Surgical resection
   d. Transarterial chemoembolization

8. In the phase III SHARP trial, sorafenib was associated with an overall survival of:

   a. 8.9 months
   b. 9.6 months
   c. 10.7 months
   d. 11.1 months

9. In the phase III SEARCH trial, sorafenib plus erlotinib was associated with significantly superior overall survival as compared with sorafenib alone.

   a. True
   b. False

10. Which agent is a monoclonal antibody directed against the VEGF receptor 2?

    a. Everolimus
    b. Mapatumumab
    c. Ramucirumab
    d. Tivantinib

Evaluation Form: Extending Survival With the Use of Targeted Therapy in the Treatment of Hepatocellular Carcinoma

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives
After participating in this activity, I am now better able to:

1. Evaluate the latest data regarding the efficacy outcomes associated with HCC therapies	1 2 3 4 5
2. Implement strategies to incorporate new and emerging agents into the treatment of HCC	1 2 3 4 5
3. Compare the results of clinical trial data of targeted therapy in HCC	1 2 3 4 5
4. Identify HCC patients in clinical practice who are appropriate candidates for ongoing clinical trials of new and emerging targeted agents	1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.
❒ I need more information before I can implement new strategies/skills/information into my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

What strategies/changes do you plan to implement into your practice? _____

_____

How confident are you that you will be able to make this change?
❒ Very confident ❒ Unsure
❒ Somewhat confident ❒ Not very confident

What barriers do you see to making a change in your practice? _____

_____

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

The content presented:

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in health care	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence	1 2 3 4 5
Provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc)	1 2 3 4 5
My opportunity for learning assessment was appropriate to the activity	1 2 3 4 5

Handout materials were useful: ❒ Yes ❒ No ❒ No handouts for this activity

Would you be willing to participate in a post-activity follow-up survey? ❒ Yes ❒ No

Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

_____

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 9317**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Request for Credit (*required fields)

Name* _____ Degree* _____

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City, State, ZIP* _____

Telephone _____ Fax _____ Email* _____

Signature* _____ Date* _____

For Physicians Only: I certify my actual time spent to complete this educational activity to be:
❒ I participated in the entire activity and claim 1.25 credits.
❒ I participated in only part of the activity and claim _____ credits.

Project ID: **9317**