
Hepatocellular Carcinoma

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Introduction

The incidence of hepatocellular carcinoma (HCC) has increased dramatically in the United States despite decreasing rates of most other malignancies.¹ HCC is now the leading cause of death in persons with compensated cirrhosis.² Worldwide, HCC is the fifth most common cancer in men and the eighth most common in women. Five-year survival rates are quite low.³ HCC occurs in persons with chronic liver disease, most often in the setting of cirrhosis. Several large studies have noted that, once cirrhosis develops, the incidence of HCC is approximately 1.4 to 3.3% per year, regardless of cause.⁴

Liver Diseases Predisposing to Hepatocellular Carcinoma

Hepatitis C virus (HCV) infection is responsible for a majority of HCC in Western countries and Japan.⁵ In the United States, many cases of HCV are related to injection drug use and blood transfusions from the 1960s to the 1980s. Given the lag time to the development of HCC, it has been estimated that the incidence of HCV-related HCC in the United States will peak around 2030.⁶

Alcohol is a significant cause of cirrhosis in Western countries and may contribute to 15 to 45% of HCC cases, although it has been difficult to separate the effects of alcohol from those of the hepatitis viruses. In the United States, alcohol abuse is five times more prevalent than HCV infection, and by some estimates is responsible for more HCC than HCV infection.⁴ Alcohol abuse is thought to be synergistic with HCV infection in promoting cirrhosis and hepatocarcinogenesis. Cirrhosis is almost always present when HCC develops as a result of alcohol abuse, and abstinence from alcohol after the appearance of cirrhosis does not decrease the risk of HCC.

Non-alcoholic fatty liver disease (NAFLD) affects approximately 30% of Americans,⁷ and 5.7% have non-alcoholic steatohepatitis, which can lead to progressive liver injury. It was recently recognized that approximately 0.5% of persons with NAFLD develop HCC.⁸ Moreover, the relative risk for HCC was found to be 4.52 in morbidly obese (BMI > 35) individuals, and diabetes doubles the risk of developing HCC.⁹ The metabolic syndrome is also synergistic in increasing the risk of HCC in persons with chronic liver disease due to viral hepatitis or alcohol.¹⁰

Early studies of patients with iron overload from hereditary hemochromatosis (HH) estimated a nearly 200-fold increase in the risk of HCC compared with age-matched controls, but more recent studies have shown a pooled HCC prevalence of 10% in HH patients. The vast majority of HCC in HH develop in the context of cirrhosis.¹¹ There is also evidence of increased HCC risk in conditions of iron overload from causes other than HH, such as β -thalassemia and the syndrome of African iron overload. Other causes of chronic liver disease associated with HCC in the context of cirrhosis include autoimmune hepatitis, Wilson's disease, alpha-1 anti-trypsin deficiency, and primary biliary cirrhosis.

Hepatitis B virus (HBV) infection is the exception to the rule of cirrhosis preceding HCC. Approximately 30 to 40% of HCC cases in patients with HBV develop in the absence of cirrhosis.¹²⁻¹⁴ Several factors have been found to increase the risk of HCC in patients with HBV, including consumption of food contaminated with aflatoxin, a mutagen produced by the fungus *Aspergillus*, co-infection with hepatitis D virus, male gender, alcohol abuse, and concomitant HCV infection.

Trends in the Incidence of HCC

The incidence of HCC is on the rise in the United States. A recent study from the Veterans Administration found that the contributions from HBV infection and alcohol abuse were relatively stable over time. Most of the increase was due to HCV-related cirrhosis.¹⁵ The rise in NAFLD also seems to be a contributing factor.¹⁶

Molecular Mechanisms of Hepatocarcinogenesis

HCC is thought to evolve along a multi-step process, where dysplastic nodules develop in the cirrhotic liver, progressing to HCC with an accumulation of genetic mutations. The emergence of neoplasia requires several elements, including self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of apoptosis, limitless replicative potential, tissue invasion and metastasis, and sustained angiogenesis.¹⁷

Mutations in DNA and hepatocyte proliferation are common to models of hepatocarcinogenesis. Activation of inflammatory pathways and hepatocyte regeneration have been implicated in the development of HCC in a number of chronic liver diseases.¹⁸ In addition, common causes of liver disease produce oxidative stress, which induces growth and survival signaling pathways as well as inducing mutations through the production of free radicals. A variety of oncogenes are variably found to be mutated in HCC, including c-Myc, the hepatocyte growth factor (and receptor c-Met) pathway, and the ErbB receptor family (a tyrosine kinase growth factor receptor family with ligands such as TGF- α). Genomic instability is another important factor in the acquisition of DNA alterations which lead to HCC.

There have been recent advances in identifying “molecular signatures” to HCC in an effort to distinguish different malignant patterns associated with different etiologies. These studies use microarrays to assess a large number of genes and a technology that might provide prognostic information and guide therapeutic interventions in the future.¹⁹

Diagnosis of HCC

Ideally, HCC should be diagnosed in patients with small tumors who are candidates for therapy. Unfortunately, however, HCC is frequently diagnosed late in its course because of the absence of pathognomonic symptoms. As a result, many patients have untreatable disease when first diagnosed.²⁰ The median survival following diagnosis is approximately 6 to 20 months.²¹ Large tumor size, vascular invasion, poor functional status, and nodal metastases are all associated with a poor outcome.

Clinical Features

Patients with HCC typically have no symptoms other than those related to their chronic liver disease. Suspicion for HCC should be heightened when patients with compensated cirrhosis develop signs of decompensation.²² When present, symptoms in patients with HCC include upper abdominal pain, weight loss, early satiety, or a palpable abdominal mass. Other uncommon symptoms are obstructive jaundice caused by invasion of the biliary tree, compression of the intrahepatic duct, or rarely, as a result of hemobilia, diarrhea, bone pain, or dyspnea due to metastases, and intraperitoneal bleeding due to tumor rupture. Tumor rupture is often associated with severe abdominal pain and hypotension, and is most commonly diagnosed by peritoneal lavage and laparotomy. CT scan typically demonstrates a liver mass and free intraperitoneal blood.

Angiography and embolization of the bleeding vessel can be an effective method of managing this life-threatening complication.

Laboratory examination is usually nonspecific. The diagnosis of HCC typically is made when an imaging study is performed to evaluate symptoms or during screening and surveillance of patients who are at risk for HCC. Imaging studies such as triple-phase CT and contrast-enhanced MRI have evolved to the extent that biopsy of liver lesions is generally reserved for select ambiguous circumstances.

Screening for HCC

Patients with longstanding HBV infection (Asian males ≥ 40 years old and females ≥ 50 years old, and Africans ≥ 20 years old) or cirrhosis from any cause are at risk for developing HCC. There is one randomized Asian trial that supports the widespread application of screening for HCC, and several prospective cohort studies suggest a survival benefit when HCC is diagnosed as part of a screening/surveillance program.²³ The AASLD recently reviewed the evidence supporting screening and surveillance for HCC and identified populations at risk.²⁴ Based on a careful review of the available evidence, the AASLD guidelines recommend screening for HCC using ultrasonography every 6 to 12 months. Because alpha-fetoprotein (AFP) has suboptimal performance characteristics as a screening tool for HCC, the AASLD guidelines recommend measuring AFP every 6 to 12 months only when ultrasonography is not available.

Imaging Studies

Ultrasound

Although ultrasound cannot distinguish HCC from other solid tumors in the liver, it is widely available, noninvasive, and commonly used for screening patients for HCC. Ultrasonography has the added benefit of assessing patency of the hepatic blood supply and the presence of vascular invasion by the tumor. In addition, ultrasound can be used intraoperatively to detect small tumor nodules during hepatic resection.

Sonographic characteristics of a hepatic lesion that are suggestive of HCC include poorly defined margins and coarse, irregular internal echoes. Small tumors are often hypoechoic. As the tumor grows, the echo pattern tends to become isoechoic or hyperechoic, and HCC can be difficult to distinguish from the surrounding liver.²⁵ Visualization may be challenging for lesions under the right hemidiaphragm, with overlying bowel gas, and in obese patients.

The accuracy of ultrasound for detecting HCC has been evaluated in several reports.^{26,27} In a large prospective study of noncirrhotic HBV carriers, the sensitivity, specificity, and positive predictive value of ultrasound were 71%, 93%, and 15%, respectively.²⁸

New ultrasound technologies, especially the use of ultrasound contrast agents, may improve the accuracy of this modality in the diagnosis of HCC.²⁹ These contrast agents have yet to be approved by the Food and Drug Administration for use in the United States. Given the low positive predictive value, a suspicious lesion observed on ultrasound requires additional studies to confirm the diagnosis and stage the tumor.

Computed Tomography

Computed tomography (CT) of the liver is one of the modalities used to evaluate an abnormality detected on ultrasound. The ability of CT to detect HCC has improved with the development of helical CT technology. This technique involves the rapid administration of contrast material in combination with extremely fast imaging. The arterial phase of enhancement allows for detection of hypervascular HCC lesions as small as 3 mm. The sensitivity of helical CT for detecting HCC may be as high as 90%; however, its accuracy has not been confirmed with explant correlation.

Some tumors are isoattenuating on both arterial and portal phase imaging and may be missed. The addition of delayed phase imaging (triple-phase helical CT) improves detection of these tumors.¹⁹ Greater sensitivity can also be achieved by using intraarterial lipoidal, a contrast agent (sensitivity between 93% and 97%). However, this technique is not commonly used, given the need for intra-arterial injection.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has the advantage of achieving high-resolution images of the liver without the use of ionizing radiation. Recent reports regarding the development of nephrogenic systemic fibrosis following intravenous gadolinium administration to patients with end-stage renal disease has tempered enthusiasm for using this modality in patients with advanced renal disease.³⁰

HCC appears as a high-intensity pattern on T2-weighted images and a low-intensity pattern on T1-weighted images. However, MRI has better sensitivity and specificity compared with CT and ultrasound in cirrhotic patients in whom it can be difficult to distinguish HCC from regenerative nodules.³¹

MRI angiography permits acquisition of a three-dimensional data set within a single breath-hold, incorporating arterial, portal venous, and late venous phases. A study comparing this technique with triphasic CT (in which pathologic examination of the explanted liver represented the gold standard) found that it had higher sensitivity for HCC nodules that were ≤ 10 mm (76% versus 61%).³²

MRI may also be beneficial in cases in which CT results are ambiguous, particularly when the liver is extremely nodular, since MRI can better differentiate dysplastic nodules from HCC. MRI may also be superior to CT in distinguishing vascular lesions, such as an hemangioma and focal fat from HCC.

AASLD Diagnostic Algorithm to Evaluate a Liver Nodule Detected in a Cirrhotic Patient

Liver nodules that exceed 2 cm in greatest diameter and enhance in the arterial phase of a triple-phase CT or gadolinium-enhanced MRI and washout in the portal venous phase are more than likely HCC. The specificity of diagnosing HCC is increased if AFP exceeds 200 ng/ml. A single imaging study from a center with state of the art equipment and experienced radiologists that shows a lesion with characteristic arterial phase enhancement and portal venous phase washout may be sufficient to establish the diagnosis of HCC. On the other hand, lesions > 2 cm that do not enhance in the arterial phase using a dynamic imaging modality should be biopsied to confirm HCC. In addition to HCC, these lesions might represent dysplastic nodules, regenerative nodules, areas of confluent fibrosis, or metastatic disease. As a general rule, patients with a negative biopsy of a liver nodule should be monitored very closely with imaging studies and repeat tissue sampling if necessary, given the risk of false-negative biopsies.

Lesions between 1 and 2 cm in diameter that have a typical vascular pattern on two dynamic imaging studies can be assumed to be HCC. On the other hand, lesions with an atypical vascular pattern or discordant vascular pattern should be biopsied. If the biopsy is nondiagnostic, the patient should undergo close surveillance and repeat biopsy if necessary.

Lesions < 1 cm should be monitored with serial imaging studies every 3-4 months. If they are stable or regress, patients can enter into standard surveillance after 6-12 months. Alternatively, lesions that grow can be evaluated according to their size and imaging characteristics as outlined above.

This diagnostic algorithm for lesions < 2 cm has recently been prospectively validated.³³

Staging

The most important factors predicting survival in patients with HCC are tumor size and the severity of underlying liver disease. The most commonly used staging systems take both of these variables into consideration.³⁴ The Okuda system incorporates the Child–Turcot Pugh Score (reflecting liver function and manifestations of portal hypertension), cancer burden, and serum AFP. Another scoring system was derived by the Cancer of the Liver Italian Program (CLIP). Prospective validation of this system suggested that it was superior to the Okuda system for predicting survival. In one report, the median survival rates for patients with CLIP stages 0, 1, 2, 3, 4, and 5-6 were 31, 27, 13, 8, 2, and 2 months, respectively.³⁵ In addition, the Barcelona Clinic Liver Cancer group has developed a validated prognostic system that incorporates patient performance status, severity of liver disease, and tumor parameters.³⁶ Determination of prognosis using the MELD scoring system in HCC patients has also been used as an accurate staging system in Asian patients, mostly with hepatitis B infection.³⁷

Treatment of Hepatocellular Carcinoma

Given the complexity of treatment options in patients with varying degrees of hepatic decompensation, it is advantageous for patients with HCC to be managed at centers with dedicated multidisciplinary teams that include hepatologists, surgeons, interventional and body imaging radiologists, and oncologists. The choice of treatment modalities should take into consideration both tumor characteristics and liver function. Surgical options (resection and orthotopic liver transplantation) are favored, and when available, liver transplantation likely results in a higher probability of long-term survival. Other curative strategies include radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI). Transarterial chemoembolization (TACE) has also been demonstrated to improve survival in patients with more advanced HCC. Several other therapeutic methods, such as intra-arterial radiation and external beam radiation, are frequently used to treat HCC; however, these modalities have been subjected to less rigorous validation.

Liver Resection

In select patients with HCC, surgical resection can result in 5-year survival rates that exceed 70%. Resection is typically well tolerated in non-cirrhotic patients with HCC, whereas patients with cirrhosis need to be carefully selected in order to reduce the risk of postoperative hepatic decompensation and subsequent morbidity and mortality.

Child–Turcot Pugh class A cirrhotic patients are candidates for surgical resection if they have preserved hepatic function without portal hypertension (wedged hepatic portal venous pressure gradient of <10 mm Hg) and a solitary HCC confined to the liver without radiographic evidence of hepatic vascular invasion.³⁸ Although there is no specific size limit, large tumor size is often associated with microvascular invasion and multifocal disease, which are risk factors for tumor recurrence. Improved preoperative imaging techniques and modalities such as intraoperative ultrasound to identify multifocal disease are helpful to improve patient selection.

The 5-year recurrence rate following resection of patients with HCC ranges from 38 to 68%, and the 5-year survival is approximately 30%. Five-year survivals as high as 50 to 90% have been reported in carefully selected patients.^{39,40} However, patients with underlying cirrhosis or chronic viral hepatitis remain at risk for recurrent disease and thus may have a less favorable prognosis.

Postoperative Adjuvant Therapies

Postoperative chemotherapy or interferon do not provide a survival benefit. A trial using intrarterial iodinated lipiodol (131I-lipiodol) in Asian patients (mostly with hepatitis B infection) demonstrated lower rates of tumor recurrence and improved postoperative survival.⁴¹ In addition, a Japanese trial using acyclic retinoids following hepatic resection reduced tumor recurrence and improved survival.⁴² Limited availability has prevented widespread use of this agent. It is anticipated that novel targeted therapies will have a role in prevention of tumor recurrence following hepatic resection.

Liver Transplantation

Liver transplantation (OLT) has the advantage of removing the tumor and treating cirrhosis, which is a premalignant condition. Careful patient selection has improved disease-free survival. Survival following OLT for patients with tumors that meet the following criteria can exceed 70% at 5 years^{43,44}:

- Solitary tumor 5 cm or less in diameter.
- No more than three tumor nodules, each less than 3 cm.
- No preoperative evidence of tumor invasion of blood vessels, lymph nodes, or extrahepatic metastasis.

Achievement of such promising results depends on a short waiting period between the diagnosis of HCC and transplantation. Longer waiting periods can lead to tumor progression with waiting list dropout rates as

high as 25%.⁴⁵ In the United States, the United Network of Organ Sharing has therefore allocated a MELD priority score of 22 for patients with HCC who meet the criteria detailed above. The score is increased every 3 months to reflect an additional 10% risk of mortality. This allocation policy requires continued analysis in order to make sure that patients with HCC are not being transplanted in favor of non-HCC patients or whether HCC patients are disadvantaged.

Although most liver transplant programs treat tumors in order to reduce the risk of tumor progression on the waiting list, there are no controlled trials that support this practice.

There have been efforts to modestly expand the selection criteria for liver transplantation for HCC. This is a very controversial issue that has not been resolved, and will likely require careful prospective validation. Ultimately, tumor biology will likely define the outcome with liver transplantation and response to other treatment modalities.

Tumor Ablation

Ablative techniques (radiofrequency ablation and percutaneous ethanol ablation) are frequently used to treat small tumors by locally ablating the lesions percutaneously. In select patients, outcomes are similar to surgical resection; however, randomized controlled trials comparing these techniques to resection or liver transplantation have not been performed.

Radiofrequency ablation involves the local application of radiofrequency (RF) thermal energy to the lesion, thereby causing tumor necrosis. This approach was evaluated in a prospective study that included 86 consecutive patients with tumors ≤ 3 cm (the majority of whom were Child–Pugh class A with HCV) who were treated with either PEI or RF ablation.^{46,47} Complete tumor necrosis occurred more often following RF ablation (90% versus 80%), although results were not statistically significant. On average, fewer treatment sessions were required for RF ablation (1.2 versus 4.8). However, complications including bleeding, pleural effusions, cholecystitis, and hemobilia occurred more frequently with RF ablation (2% major and 8% minor complications for RF ablation versus none for the PEI group). Of concern is the potential for seeding along the needle track that has been reported in patients receiving RF ablation for solitary tumors.³² Based on this observation, RF ablation is often avoided for tumors that are adjacent to the hepatic capsule.

Chemoembolization

Disruption of the arterial blood supply and injection of chemotherapy (typically doxorubicin in combination with other agents) into hypervas-

cular HCC lesions has been shown to prolong life.^{48,49} Patients with multifocal disease in the absence of portal vein invasion or Child–Turcotti Pugh class C disease are typically eligible for this intervention.

Novel Systemic Chemotherapy

The United States Food and Drug Administration recently approved the raf kinase and angiogenesis inhibitor sorafenib for treatment of advanced HCC in patients not eligible for the above treatments. Unpublished data (Press Release, Onyx and Bayer Pharmaceuticals, February 2007) show a modest survival benefit in patients receiving the drug, the first systemic agent ever to have shown a survival benefit in patients with advanced HCC.

Conclusions

HCC is an aggressive tumor with a high case fatality rate. Successful treatment is contingent on early detection through widespread use of surveillance of patients at risk for HCC development. The future of treatment and early detection likely will be based on characterization of the molecular pathogenesis of this disease.

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