HEPATOCELULAR CANCER: A GUIDE FOR THE INTERNIST

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ABSTRACT

Hepatocellular cancer is the third leading cause of cancer-related deaths worldwide. Its incidence has increased dramatically in the United States because of the spread of hepatitis C virus infection and is expected to increase for the next 2 decades. Hepatitis B virus, hepatitis C virus, and chronic heavy alcohol use leading to cirrhosis of the liver remain the most important causes. The diagnosis of hepatocellular cancer rests on a combination of radiologic, serologic, and histopathologic criteria. Liver transplantation is the only definitive treatment. Resection of the tumor and other percutaneous therapies are more commonly used in practice, because most hepatocellular cancers are detected at an advanced stage. Patients who are at high risk for the development of hepatocellular cancer should be screened with an ultrasound of the liver every 6 months. The prognosis is dependent on both the underlying liver function and the stage at which the tumor is diagnosed. The aim of this review is to familiarize internists in screening, diagnosis, and referral of patients with hepatocellular cancer in an appropriate and timely fashion. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Hepatocellular cancer; Hepatitis C; Chronic alcoholism; Cirrhosis; Screening

Hepatocellular cancer is the fifth most common cause of cancer and the third leading cause of cancer-related deaths worldwide.1 Its incidence has increased dramatically in the past few years in the United States and other Western countries.2 Despite advances in surgical and nonsurgical therapies in the treatment of hepatocellular cancer, a number of controversial issues regarding appropriate screening methods, diagnosis, staging, and management continue to evolve. The aim of this review is to help the internist identify high-risk patients, implement an appropriate screening strategy, order relevant tests to confirm the diagnosis, and formulate an appropriate management plan.

EPIDEMIOLOGY

Hepatocellular cancer is a major health problem; more than half a million cases are reported yearly worldwide. The geographic areas most affected are located in Southeast Asia and sub-Saharan Africa. More recently, an increasing number of cases have been identified in Western countries.

A large, retrospective cohort study confirmed an almost 2-fold increase in the incidence of hepatocellular cancer from 1975 to 1998 in the United States.2,3 This increase is primarily related to the spread of hepatitis C virus (HCV) infection, which peaked in the United States in the late 1980s.4 Given the time lag of 2 to 4 decades between the onset of infection and the development of cirrhosis, it has been predicted that the incidence of hepatocellular cancer will continue to increase over the next 2 decades.4 According to the American Cancer Society, there will be 19,160 new cases diagnosed and 16,780 deaths due to this disease in the United States in 2007.5

Males are more commonly affected than females in the ratio of 3:1 to 9:1.6 The mean age of presentation of hepatocellular cancer in Europe and the United States is approximately 60 years.7 This is in contrast with patients in Asia and Africa, where it is between 20 and 50 years.

CAUSE

The major clinical risk factor for the development of hepatocellular cancer is cirrhosis of the liver. Chronic infections with hepatitis B virus (HBV) and HCV and chronic heavy alcohol use are the most important risk factors for the
development of cirrhosis. HBV accounts for the majority of hepatocellular cancer in China and Africa, where most of the infection is acquired early in life either from mother to the offspring or by horizontal transmission. In contrast, HCV accounts for most of the cases in the Western hemisphere. Chronic alcohol use of greater than 80 g per day for more than 10 years increases the risk of hepatocellular cancer 5-fold. Furthermore, chronic alcohol use in HBV or HCV infection doubles the risk of hepatocellular cancer over either infection alone.

The magnitude of risk of hepatocellular cancer from cirrhosis due to other causes is not well known. There have been reports in patients with hereditary hemochromatosis, alpha-1 antitrypsin deficiency, and autoimmune hepatitis. An increased incidence has been associated with smoking and exposure to aflatoxin, a mycotoxin that contaminates peanuts and soybeans, and causes mutations in the p53 tumor suppressor gene. Approximately one quarter of all cases diagnosed in the United States do not have any of these risk factors. There is growing interest in the role of insulin resistance syndrome as a risk factor for these cryptogenic cases. Insulin resistance syndrome is present in virtually all cases of nonalcoholic fatty liver disease; this condition is thought to predispose to nonalcoholic steatohepatitis and cirrhosis in 10% to 20% of cases. Diabetes and obesity, 2 major manifestations of insulin resistance syndrome, have been shown to double the risk of hepatocellular cancer (Table 1).

### CLINICAL FEATURES

The typical clinical manifestations of hepatocellular cancer are right upper quadrant abdominal pain, early satiety, and weight loss. However, more and more hepatocellular cancers are now detected at an asymptomatic stage because of the growing awareness of these tumors in patients with chronic liver disease and cirrhosis. Other clinical presentations, such as spontaneous rupture of the tumor into the peritoneal cavity, obstructive jaundice, and bony pain from metastasis, are extremely uncommon. Various paraneoplastic syndromes have been associated with hepatocellular cancer. These include erythrocytosis (erythropoietin), hypoglycemia (insulin-like growth factor), and hypercalcemia (parathyroid-related protein). Physical findings in patients with hepatocellular cancer generally reflect the severity of the underlying chronic liver disease and cirrhosis. The liver may be enlarged and a vascular bruit is sometimes heard, consistent with hypervascularity of the tumor.

### DIAGNOSIS

A consensus statement from the European Association for the Study of Liver Diseases (EASL) has been formulated to help clinicians standardize diagnostic approaches (Table 2).

### Lesions Greater Than 2 Centimeters in Diameter

In nodules greater than 2 cm diameter in size, a diagnosis of hepatocellular cancer can be made if any 2 imaging studies (including ultrasonography, computed tomography, magnetic resonance imaging, or hepatic arteriography) show increased vascularity. Alternatively, only 1 imaging study (including ultrasonography, computed tomography, magnetic resonance imaging, or hepatic arteriography) show increased vascularity. Our ability to diagnose these tumors noninvasively rests on the premise that they are seen on a background of cirrhosis and enhance with contrast on rapid-sequence imaging secondary to their neovascularity. These radiologic criteria for diagnosis have excellent diagnostic accuracy with reported sensitivity of 100% and specificity of 98.8%. In cases of indeterminate radiologic findings, fine-needle aspiration biopsy is recommended.

### Lesions Less Than 2 Centimeters in Diameter

Imaging techniques for lesions less than 2 cm do not have sufficient accuracy in distinguishing hepatocellular cancer from other conditions. Alpha-fetoprotein levels may be normal or only slightly elevated and thus provide no diagnostic utility. Hepatic lesions less than 1 cm in size have a less than 50% chance of being malignant, and serial ultrasound
(every 3 months) is recommended. On the other hand, fine-needle aspiration biopsy should be performed in lesions between 1 and 2 cm in size.

Role of Liver Biopsy
The role of liver biopsy has been the subject of great controversy. For almost all other types of cancer, histopathologic confirmation is necessary to make a diagnosis. However, as elucidated in Table 2, both the EASL and United Network for Organ Sharing criteria do not require a biopsy for the diagnosis of hepatocellular cancer in lesions greater than 2 cm. For lesions less than 2 cm in size where high-quality imaging or expertise in reading these images is not available, a biopsy is recommended.

There is a small but definite risk of tumor seeding from an invasive biopsy. The prevalence rates have been reported to be anywhere between 0.003% and 5%. However, it is unclear whether it leads to metastatic disease or worse survival because a majority of patients are treated by excision of the subcutaneous tumor deposit. Also, the false-negative rate from biopsy of lesions less than 2 cm is approximately 30% to 40%. Thus, a negative biopsy does not conclusively rule out the diagnosis of hepatocellular cancer.

Role of Serum Markers
The 3 most commonly used serum markers are alpha-fetoprotein, Lens culinaris agglutinin-reactive alpha-fetoprotein (alpha-fetoprotein-L3), and protein induced by vitamin K antagonist-II. The sensitivity and specificity of these markers to diagnose hepatocellular cancer vary according to the threshold level used. Total alpha-fetoprotein has a sensitivity of 60% and specificity of 90% at cutoff values between 10 and 20 ng/mL. A systematic review confirmed the poor diagnostic ability of alpha-fetoprotein alone in detecting hepatocellular cancer at any level of pretest risk. It is a much better diagnostic test in the presence of a hepatic mass where a cutoff value of greater than 400 ng/mL is used in combination with imaging criteria. An increase in the percentage of alpha-fetoprotein-L3 over the total alpha-fetoprotein (>10%) is specific for small hepatocellular cancer. Protein induced by vitamin K antagonist-II is also more specific than total alpha-fetoprotein in detecting hepatocellular cancer. However, these are not available in most nonresearch laboratories in the United States at this time.

SCREENING
Although there is no definite evidence that screening in hepatocellular cancer improves survival, many physicians screen patients in high-risk groups with either serum alpha-fetoprotein or ultrasound of the liver or both. Two recent randomized controlled trials completed in China demonstrated a significant reduction in hepatocellular cancer-related mortality in patients who underwent screening. Ultrasound of the liver is the preferred screening test because it has a sensitivity of 84% and specificity of more than 90%. A combination of alpha-fetoprotein and ultrasound has been reported to increase the sensitivity by 5% to 10% over ultrasound alone, but it also increases costs and false-positive rates.

The United States Preventive Services Task Force, National Comprehensive Cancer Network, and American Cancer Society do not have any specific guidelines for screening patients for hepatocellular cancer. The National Cancer Institute recommends against routine screening for lack of a survival benefit. The American Association for the Study of Liver Diseases and EASL recommend ultrasound of the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Diagnostic Criteria for Hepatocellular Cancer</th>
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</thead>
<tbody>
<tr>
<td>1. Histopathologic criteria</td>
<td></td>
</tr>
<tr>
<td>2. Noninvasive criteria (limited to patients with underlying cirrhosis)</td>
<td></td>
</tr>
<tr>
<td>(i) European Association for the Study of Liver Diseases Criteria:</td>
<td></td>
</tr>
<tr>
<td>(a) Radiologic criteria: Two coincident imaging techniques that identify a focal lesion more than 2 cm showing arterial hypervascularization</td>
<td></td>
</tr>
<tr>
<td>(b) Combined criteria: One imaging modality that identifies a focal lesion more than 2 cm in diameter showing arterial hypervascularization AND serum AFP levels greater than 400 ng/mL</td>
<td></td>
</tr>
<tr>
<td>(ii) United Network for Organ Sharing Criteria (for listing patients on transplant list):</td>
<td></td>
</tr>
<tr>
<td>(a) A prelisting biopsy is not necessary</td>
<td></td>
</tr>
<tr>
<td>(b) US of the liver, a CT or MRI scan of the abdomen that documents the tumor, and a CT of the chest that rules out metastatic disease with any 1 of the following:</td>
<td></td>
</tr>
<tr>
<td>➢ a vascular blush corresponding to the area of suspicion seen on the above imaging studies</td>
<td></td>
</tr>
<tr>
<td>➢ an alpha-fetoprotein level of &lt;200 ng/mL</td>
<td></td>
</tr>
<tr>
<td>➢ an arteriogram confirming a tumor</td>
<td></td>
</tr>
<tr>
<td>➢ a biopsy confirming hepatocellular cancer, prior chemoembolization of lesion, radiofrequency, cryoablation, or chemical ablation of the lesion</td>
<td></td>
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</tbody>
</table>

AFP = alpha-fetoprotein; US = ultrasound; CT = computed tomography; MRI = magnetic resonance imaging.
liver every 6 months for high-risk patients.\(^{42}\) (Table 3 and Figure 1).

### NATURAL HISTORY AND PROGNOSIS

Prospective studies have shown that most hepatocellular cancers develop through a progressive pathway from pre-malignant nodular lesions to cancerous lesions in the cirrhotic liver.\(^ {43}\) Progression takes an average of approximately 2 to 4 decades from the initial time of infection with HBV or HCV to the development of cirrhosis. Thereafter, the annual risk of hepatocellular cancer is 2% to 3% for HBV, 1% to 7% for HCV, and 1% for alcohol-induced cirrhosis.\(^ {10,44}\) Hepatocellular cancer can develop in the absence of cirrhosis in patients with HBV infection at a rate of 0.26% to 0.6% per year.\(^ {44}\) Recent studies have shown that treatment of chronic HCV infection with interferon monotherapy in patients with cirrhosis decreases the risk of hepatocellular cancer, and it is expected that combination therapy with pegylated interferon and ribavirin may reduce this risk even further.\(^ {45,46}\)

Predicting survival in hepatocellular cancer is complicated by the fact that 2 disease processes, namely, the tumor and underlying cirrhosis, are present simultaneously. Numerous studies have shown that prognosis is directly proportional to the degree of hepatic function, suggesting that cirrhosis rather than mass size of the tumor is the main determinant of outcome. The median survival of untreated patients with newly diagnosed hepatocellular cancer is weeks to months.\(^ {47}\) A number of factors are associated with worse outcome: male sex, advanced age, etiologic agent

**Table 3** High-Risk Groups for Screening of Hepatocellular Cancer

<table>
<thead>
<tr>
<th>Cirrhosis:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td></td>
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<tr>
<td>Hepatitis C</td>
<td></td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
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<tr>
<td>Hereditary hemochromatosis</td>
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<tr>
<td>Primary biliary cirrhosis</td>
<td></td>
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<tr>
<td>Nonalcoholic steatohepatitis</td>
<td></td>
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<tr>
<td>Patients waiting on the liver transplant list</td>
<td></td>
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</table>

No cirrhosis: Chronic hepatitis B carriers: males aged >40 y and females aged >50 y, family history of hepatocellular cancer in a patient with chronic hepatitis B.

Screening for patients with cirrhosis secondary to alpha-1 antitrypsin deficiency, autoimmune hepatitis, and Wilson’s disease is considered low-moderate risk, and there are no recommendations for screening at this time.

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Figure 1: Surveillance of hepatocellular cancer in patients with cirrhosis of the liver. HCC = hepatocellular cancer; AFP = alpha-fetoprotein.
evolve. In the 1980s, poor patient selection led to dismal
tation as the primary method of treatment continue to
Liver Transplantation.

Resection of the tumor is the treatment of choice
Surgical Therapy

Because of the heterogeneous nature of hepatocellular
By the Barcelona Clinic Liver Cancer staging classification48
MANAGEMENT

The definitive treatment of hepatocellular cancer is liver
Surgical Therapy

Resection. Resection of the tumor is the treatment of choice
Liver Transplantation. The indications for liver transplan-

outcomes with 5-year survival of less than 40%.58 A land-

(HCV worse than HBV), presence of more than 1 risk
because of its cause, epidemiologic background,
and severity of hepatic dysfunction, a worldwide staging
system is not in place. The most commonly used staging
system for solid tumors, TNM classification, has severe
limitations because it does not include the severity of un-
Therefore, other staging systems such as
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Local Ablation uses image-guided chemi-
cal (ethanol, acetic acid) and thermal (radiofrequency,
cryoablation) techniques. Ablation is commonly used with
curative intent in patients with unresectable tumors, with
survival similar to resection. Percutaneous ethanol injection

Table 4 Barcelona Clinic Liver Cancer Staging Classification47

<table>
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<tr>
<th>Stage</th>
<th>Performance Status Test</th>
<th>Tumor Stage</th>
<th>Okuda Stage†</th>
<th>Liver Function Status</th>
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<tbody>
<tr>
<td>A</td>
<td>0</td>
<td>Single</td>
<td>I-II</td>
<td>Child Pugh‡ A-B</td>
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<tr>
<td>B</td>
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<td>C</td>
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<tr>
<td>D</td>
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<td>Any</td>
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For Stages A and B: All criteria should be fulfilled. For Stages C and D: At least 1 criterion must be fulfilled.
*Performance status test is based on the Eastern Co-Operative Oncology Group performance scale: 0: asymptomatic, 1: symptomatic and fully ambulatory, 2: symptomatic and in bed <50% of the day, 3: symptomatic and in bed >50% of the day, 4: bedridden.
†Okuda staging system (I-III) is another staging system that takes into account the size of the tumor, presence of ascites, and albumin and bilirubin concentrations.
‡For Child-Pugh Classification, see Table 5.

the indications for liver transplantation; this cures both the cancer and the underlying cancer-prone cirrhotic liver (Figure 2).

The assignment of priority scores for liver transplantation is based on the Model for End-Stage Liver Disease score, which uses laboratory values of serum creatinine, total bilirubin, and international normalized ratio. Patients with hepatocellular cancer are assigned a higher Model for End-Stage Liver Disease score and thus, get a priority for transplant over those with similar degrees of liver dysfunction, and without hepatocellular cancer, who are waiting for a transplant. However, a shortage of donors has led to unacceptably high dropout rates because of deaths or appearance of contraindications, with survival decreasing to less than 50% using an intention-to-treat principle.61

The majority of hepatocellular cancers identified at initial presentation are unresectable and do not qualify to be on the transplant list. A number of other options are available.

Local Ablation. Local ablation uses image-guided chemical (ethanol, acetic acid) and thermal (radiofrequency, cryoablation) techniques. Ablation is commonly used with curative intent in patients with unresectable tumors, with survival similar to resection. Percutaneous ethanol injection

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Given the difficulties in obtaining a cadaveric liver in a timely fashion, “bridging” therapies such as surgical resec-

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was the most commonly applied technique, with a response rate of 70% to 100%. However, radiofrequency thermal ablation is more commonly used now because it can achieve better control of disease and improve survival compared with percutaneous ethanol injection. The major limitation of local ablation is its inability to achieve meaningful response rates in infiltrative lesions and in tumors larger than 4 to 5 cm in size.

**Transarterial Therapy.** Transarterial interventions are available for treatment of large unresectable hepatocellular cancers that are not amenable to resection or percutaneous therapies. These are generally used with palliative intent to reduce tumor burden. The most commonly used techniques include transcatheter arterial chemoembolization and transarterial radioactive iodine with lipiodol. A systematic review of randomized trials for unresectable hepatocellular carcinoma showed that in patients with compensated cirrhosis and good functional status, arterial embolization improved 2-year survivals. Postembolization syndrome, associated with abdominal pain and fever, can sometimes occur and precipitate ascites and hepatic encephalopathy.
Patients with advanced liver disease (Child-Pugh C) and portal vein thrombosis should not undergo these therapies because of the risk of precipitating acute liver failure.

**Combination Therapy.** Combined therapy with transcatheter arterial chemoembolization followed by radiofrequency thermal ablation has been shown to produce good local response, especially in tumors less than 5 cm.70 However, the overall usefulness of this procedure needs to be established in a larger number of patients.

**Systemic Treatment.** Numerous systemic therapies, including doxorubicin, tamoxifen, megestrol, interferon alpha, and anti-androgens, have been tried and compared in randomized trials. The use of most of these agents is associated with significant toxicity without any discernible benefit with regard to survival or complete response.71,72

**FUTURE TRENDS**

Proteomics has led to the discovery of new molecular markers, such as des-gamma carboxyprothrombin and human hepatocyte growth factor, for screening hepatocellular cancer, and these are being validated for clinical use. Antiangiogenesis agents such as vascular endothelial growth factor antibodies and thalidomide, nonspecific inhibitors of carcinogenesis such as Sandostatin and arsenic, and better means of delivering radiation such as yttrium microspheres are all being actively investigated for the treatment of hepatocellular cancer. Expanding the criteria for selecting patients for liver transplantation, such as the University of California San Francisco criteria, which include a single tumor less than 6.5 cm, 3 or less nodules with the largest being less than 4.5 cm, and total tumor diameter less than 8 cm, has shown promising results and may replace the Milan criteria.73

**CONCLUSION**

The incidence of hepatocellular cancer is increasing in the Western world, including the United States. Although HBV, HCV, and alcohol use constitute the most important risk factors for the development of hepatocellular cancer, diabetes and obesity may contribute to increased carcinogenicity. Primary care physicians taking care of patients with chronic viral hepatitis and cirrhosis will need to have a heightened awareness of hepatocellular cancer, because the translation of bench research into clinical practice will lead to newer diagnostic tests, better therapeutic options, and improved survival of these patients. Finally, an important frontier in the battle against hepatocellular cancer will be the application of effective preventive strategies aimed at decreasing the risk of transmission of HBV and HCV, and the development of safe and effective medications for the treatment of chronic HBV and HCV.

**ACKNOWLEDGMENTS**

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**References**


