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Hepatocellular Carcinoma



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Hepatocellular carcinoma (HCC) is the second most common cause of death worldwide from liver cancer. HCC is typically seen in underlying cirrhosis secondary to viral hepatitis, which is common risk factor. While direct acting antivirals may reduce the development of HCC due to hepatitis C in upcoming years, the increasing incidence of nonalcoholic fatty liver disease (NAFLD) make the trend of HCC difficult to predict. Surveillance for HCC should be performed in high risk patients. The diagnosis of HCC can be made radiographically in the majority of cases. There are many factors that determine the appropriate treatment for patients with HCC including underlying liver disease, size, number of lesions, vascular involvement and extravascular disease. The treatment of early stage and advanced disease is fairly clear. Further studies are needed to help refine the best treatment options in patients with early-, intermediate-, and late-stage disease who are either neither transplant candidates or unresectable.

INTRODUCTION

Primarily liver cancer is the fifth most common cancer in men and ninth most common in women, accounting for 554,000 and 228,000 cases, respectively.¹ Hepatocellular carcinoma (HCC) accounts for over 90% of all primary liver cancers. In most areas, its incidence is therefore a close approximation of the incidence of hepatocellular carcinoma.² While the highest rates of liver cancer are in Africa and Asia, the incidence in the United States is also alarming.¹ There will be an estimated 33,190 new cases of liver cancer diagnosed in the United States this year alone with approximately 23,000 deaths.³ The incidence of HCC in the United States varies with age, gender and race.

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The highest incidence is in those older than 65 years, males, Asians and Pacific Islanders.⁴ The median age at diagnosis is 63 years.³ Historically, the incidence of HCC has continued to climb through the years as has the mortality. Although the mortality rates continued to increase in the United States between 2007 and 2010, there was no significant increase in the incidence of HCC.⁴ With current screening guidelines as well as improved and well-tolerated treatments for hepatitis C now available, there is hope that both the incidence and mortality from HCC will decrease.

Risk Factors

HCC usually develops in the background of underlying cirrhosis.⁵ The risk of developing HCC in patients with cirrhosis increases depending on the etiology of the cirrhosis. These etiologies include hepatitis C, hepatitis

B, hereditary hemochromatosis, Wilson's disease, autoimmune hepatitis, alpha-1 antitrypsin, primary biliary cirrhosis (PBC), alcohol and non-alcoholic steatohepatitis-induced cirrhosis. Furthermore, risk factors specific to the etiologies can increase the incidence of HCC even higher.

Overall, the 5-year cumulative risk of developing HCC ranges from 4% in patients with primary biliary cirrhosis to 30% in those with cirrhosis from chronic hepatitis C infection.⁶ The stage of cirrhosis also correlates with the risk of developing HCC.⁶ There is an estimated 4-fold increased risk of developing HCC in those with cirrhosis as compared to those with chronic hepatitis.⁶ Approximately 80% of HCCs are attributable to chronic viral hepatitis.⁷ Even in those patients with HCC in whom cirrhosis is not present, there are typically histologic changes consistent with underlying liver disease including steatosis, varying degrees of fibrosis, dysplasia or iron overload.⁸

Patients with hepatitis C-induced cirrhosis have the highest 5-year cumulative risk of developing HCC.⁶ This incidence also varies depending on geography, where the 5-year cumulative risk is 30% in Japan and 17% in the United States and Europe.⁶ Among those with hepatitis C-induced cirrhosis, there are a subset of patients at higher risk than others. Patients with hepatitis C-induced cirrhosis who are older at diagnosis or at time of infection, males, elevated bilirubin, decreased platelets, presence of esophageal varices or physical examination findings of palmar erythema or spider angiomas have an increased risk of developing HCC.^{9,10} There is also an increased incidence of HCC in patients with hepatitis C-induced cirrhosis with comorbid conditions of porphyria cutanea tarda, hepatic steatosis, hepatitis B and alcohol use (>60g/day).¹¹⁻¹⁴ Patients who are co-infected with hepatitis C and HIV tend to be diagnosed with HCC at an earlier age and sooner after their diagnosis of hepatitis C than those infected with HCV alone.¹⁵ There does not appear to be a significant difference in the incidence of HCC based on the genotype or viral load of hepatitis C.¹⁶

Similar to patients with hepatitis C, those with hepatitis B-induced cirrhosis are at increased risk for HCC, and there is geographic disparity. The 5-year cumulative incidence of HCC among patients with hepatitis B in East Asia is 15% compared to 10% in Europe. Older age, degree of thrombocytopenia and liver firmness on physical examination are associated with an increased risk of developing HCC.¹⁷ The incidence of HCC is

also highest among those with hepatitis B-induced cirrhosis, less with chronic hepatitis B and is least common in inactive carriers.⁶ Patients with occult hepatitis B (presence of HBV DNA who are hepatitis B surface antigen-negative) are also at increased risk of developing HCC.¹⁸ While the risk associated with having a high HBV DNA or a hepatitis B e-antigen at time of diagnosis is unclear, the risk of developing HCC is lower for patients who clear hepatitis B surface antigen either spontaneously or with treatment.^{6,19} Co-infection of hepatitis B with hepatitis D increases the risk for developing HCC threefold.²⁰ Aflatoxin exposure significantly increases the risk of patients with hepatitis B developing HCC.²¹ Similar to patients with hepatitis C, there is an increased risk of HCC in patients with hepatitis B who consume alcohol.¹⁴ Patients with alcohol-induced cirrhosis, even in the absence of chronic viral hepatitis, are also at increased risk of developing HCC with a 5-year cumulative incidence of 8%.⁶ Alcohol may also have a direct carcinogenic effect on the liver and may lead to HCC even in the absence of cirrhosis.¹⁴

Patients with cirrhosis related to etiologies other than chronic viral hepatitis are also at increased risk for HCC. The degree of their risk for some of these etiologies, however, is not as well defined. The risk of developing HCC in the setting of cryptogenic cirrhosis has been reported by Marrero et al to be as high as 29%.²² Among these patients, however, a significant proportion of these patients may have underlying non-alcoholic fatty liver disease (NAFLD).²² In their study, NAFLD accounted for up to 13% of the patients with HCC.²² While this incidence may be an overestimate, with an estimated prevalence of 30-40% in the United States and 6-35% worldwide, NAFLD is an important risk factor in the development of HCC.²³ There are data to suggest that the duration of cirrhosis may be longer in patients with NAFLD-related cirrhosis.^{24,25} There also appears to be an association with obesity and the risk of development and death from HCC.^{26,27} The risk of developing HCC is twice as high among patients with diabetes.²⁸

Even among metabolic liver diseases, there is a wide range in the risk of HCC. While the risk of developing HCC among patients with Wilson's disease is extremely low, the 5-year cumulative incidence among patients with hereditary hemochromatosis is 21%.²⁹ The risk of developing HCC in patients with alpha-1 antitrypsin deficiency only increases once they develop cirrhosis.³⁰

Similarly, patients with primary biliary cirrhosis are at increased risk with advanced fibrosis.³¹ HCC is seen predominantly in men with PBC, and the overall 5-year cumulative incidence is 4%.³¹ Cardiac congestive liver fibrosis is not thought to be a typical risk factor in the development of HCC, this has been reported in the literature.³² Coffee consumption is one well-studied association that actually decreases the risk of HCC.³³ Recognizing the risk factors for the development in HCC is paramount in the surveillance, prevention and early recognition of the disease for improved outcomes.

Surveillance

The decrease in mortality with surveillance, the noninvasive means of testing and the difference between early and late detection are key factors as to why surveillance for HCC is recommended in high-risk patients by the American Association for the Study of Liver Diseases (AASLD).³⁴ It has been reported that biannual alpha fetoprotein (AFP) and ultrasound imaging decreases the mortality from HCC by 37% in patients with past or present hepatitis B infection.³⁵ The benefit of surveillance is also supported by data that show the poor prognosis in patients in whom the diagnosis is made only after they are symptomatic.³⁶

The two most well-studied serologic markers for detection of HCC are AFP and descaboxiprothrombin (DCP), also known as prothrombin induced by vitamin K absence II (PIVKA II). The difficulty in supporting AFP as a screening test is that, depending on the cut-off level, the sensitivity or specificity may be suboptimal. A case-control study evaluating its efficiency at diagnosing HCC showed that its sensitivity was approximately 60%, and its positive predictive value was only 25.1% at a 5% tumor prevalence at a value of 20ng/mL.³⁷ Raising the cut-off only decreases the sensitivity even further. There had also been some hope that PIVKA II could be an adequate serologic test used in the surveillance of HCC. However, data show that while it may be a useful diagnostic test, its role in surveillance is limited.³⁸ The sensitivity of PIVKA II was 74% at a cutoff of 40 mAU/mL.³⁹ While the use of the combination of AFP and PIVKA II increases the sensitivity in the diagnosis of HCC, the specificity is still only 74%.³⁹ Ultimately, the use of AFP, PIVKA II or the combination of the two is inadequate to recommend universally in the surveillance of HCC.³⁹ Groups continue to evaluate these in specific subset of patients. For example, a recent study showed that a combination of the PIVKA

II and AFP may aide in the early detection of HCC in patients with hepatitis B.⁴⁰ If further studies support this, guidelines may support its use. In the future, there may also be a role of various novel biomarkers to measure response to therapies.⁴¹

In addition to serologic tests, radiologic testing has also been studied for surveillance of HCC. Ultrasound is the diagnostic test of choice and is recommended by the AASLD in the surveillance for HCC.³⁴ Advantages of ultrasound include the lack of radiation associated with its use, the ease of accessibility and its relatively low cost compared to other imaging modalities. However, the disadvantages of ultrasound testing are that it is operator dependent, a likely decreased sensitivity in obese patients and the overlap of ultrasonographic appearance of other lesions in the background of cirrhosis.⁴² Thus, ultrasound sensitivity has been reported to be between 65% and 80%.⁴³ Computed tomography (CT) and magnetic resonance imaging (MRI) are not appropriate imaging modalities for surveillance because of the radiation exposure, the risks of contrast or gadolinium administration as well as the cost. Imaging with CT may be considered in obese patients in whom ultrasound is non-diagnostic.

Ideally, surveillance could be performed with a combination of serologic and radiologic tests. Unfortunately, the data do not support this. In a study of more than 9,000 patients in China, patients with hepatitis B underwent surveillance with ultrasound and AFP.⁴⁴ The false positive rate was 7.5% when combining the two modalities. Ultimately, despite its limitations, ultrasound still has a high specificity and thus, is a more appropriate test than the current serologic markers in the surveillance for HCC.⁴⁵

The AASLD recommends surveillance for HCC in high-risk patients every six months.³⁴ This recommendation is based on a study that showed a survival benefit of semiannual surveillance compared to annual surveillance in patients with hepatitis B.⁴⁶ In an attempt to simplify guidelines, the AASLD generalized these findings to all high-risk patients.³⁴ A more recent study that showed smaller, less advanced tumors were detected, and patients had longer survival when surveillance was performed every six months as opposed to every twelve months to support the AASLD guidelines.⁴⁷

Surveillance for HCC is recommended for patients at increased risk. Based on cost-effectiveness models,

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the AASLD considers that it is cost-effective to perform surveillance in patients with hepatitis B if the expected HCC risk is greater than 0.2% per or hepatitis C if the risk of developing HCC is greater than 1.5%/year,³⁴ the difference likely owing to the varying prevalence between the two etiologies. As previously mentioned, the incidence of HCC in etiologies of cirrhosis other than chronic viral hepatitis has not been clearly defined. While the guidelines do not make clear recommendations for many of these populations, it is reasonable to perform surveillance for HCC in any patient with cirrhosis until further data suggest otherwise.

There is no role of surveillance of HCC in patients with hepatitis C who do not have cirrhosis. There was a large prospective study of 12,000 men in Taiwan that showed a significant increase in the risk of developing HCC in patients with hepatitis C, although the data should be interpreted with caution as it included both cirrhotics and non-cirrhotics.⁴⁸ Another prospective study of approximately 1,000 patients estimated that the risk of developing HCC in patients with hepatitis C who are not cirrhotic to be 0.8% per year.⁴⁹ The AASLD deemed it cost effective to screen for HCC in patients with hepatitis C without cirrhosis only if the annual incidence was >1.5% per year. Thus, at this time, the evidence does not support surveillance for HCC in patients with hepatitis C who are not cirrhotic.

There are data, however, to support surveillance

of HCC in certain subsets of patients with hepatitis B. Cost-effective analysis favors surveillance in patients with hepatitis B whose risk of developing HCC is >0.2% per year.³⁴ Some of the risk factors for HCC in patients with hepatitis B have been described above. The presence or absence of these risk factors aide in the risk stratification. As in patients with hepatitis C, patients with hepatitis B with cirrhosis are at the highest risk of developing HCC and should undergo surveillance. The AASLD also recommends surveillance for adult Caucasian patients with active hepatitis B without cirrhosis, Asian male hepatitis B carriers older than 40 years, Asian females older than 50 years, hepatitis B carriers with a family history of HCC and African/North American blacks with hepatitis B.³⁴ Co-infection with hepatitis C increases the risk for HCC, though there are no guidelines regarding surveillance in this population.

Diagnosis

Unlike many other solid organ tumors, there are many situations in which HCC can be diagnosed with a high degree of accuracy based on imaging alone.⁵⁰ Specifically, four-phasic multidetector CT (unenhanced, arterial, venous and delayed phase) or dynamic contrast-enhanced MRI are used to diagnose HCC. Whether or not imaging alone is sufficient to diagnose HCC is also based on the size of the lesion, as the sensitivity and specificity of these modalities increase with increasing size of the tumor.⁵¹ Biopsy is generally avoided if



Figure 1. Hepatocellular carcinoma on CT scan in hepatic arterial phase

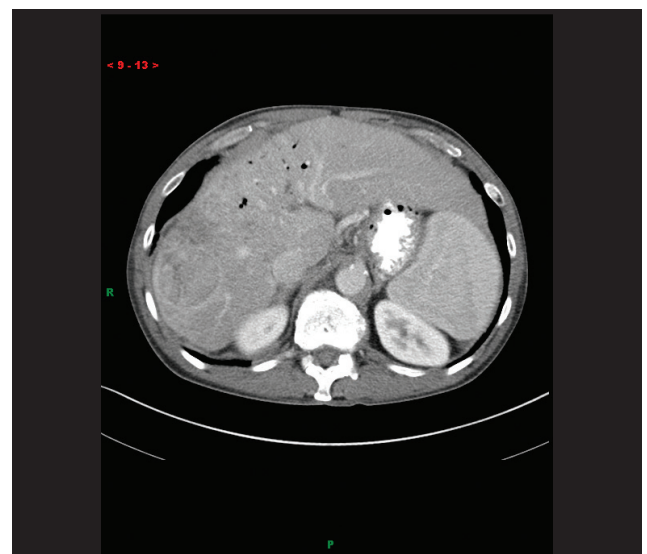


Figure 2. Hepatocellular carcinoma on CT scan in portal venous phase

Table 1. Okuda System

High risk features	-tumor size >50% of liver -presence of ascites -albumin <3 mg/dL -bilirubin >3 mg/dL
Stage I	None
Stage II	1-2 high risk features
Stage III	3-4 high risk features

Median survival:

Stage I - 11.5 months

Stage II - 3 months

Stage III - 0.9 months

(Okuda, 1985)

possible, as a meta-analysis estimates the incidence of needle tract tumor seeding to be 2.7%.⁵²

If there is concordance between contrast-enhanced ultrasound and MRI, the diagnosis of HCC can be made even if the lesion is less than 2 cm in patients with cirrhosis.⁵³ However, the use of contrast agents for contrast-enhanced ultrasound has not been FDA approved in the United States. A single contrast-enhanced study, however, appears to be sufficient to diagnose HCC in patients with cirrhosis who were found to have nodules between 1-2 cm on surveillance.⁵⁴ Thus, the AASLD does not recommend any further diagnostic testing in nodules >1 cm detected in patients at risk for HCC if there is arterial hypervascularity and venous or delayed phase washout on contrast-enhanced imaging.³⁴ (Figures 1 and 2) If there are atypical features on imaging, then either a different contrast enhanced study or liver biopsy is recommended.³⁴ For lesions less than 1 cm, the AASLD recommends serial imaging with ultrasound every three months as these lesions will likely be cirrhotic nodules.³⁴

There are limited data that show that an AFP level of > 200 ng/mL in non-African American patients with hepatitis C related cirrhosis and a hepatic mass may be diagnostic of HCC.⁵⁵ Previous data supported using this level as a cutoff to aid in the diagnosis of HCC in conjunction with imaging^{56,57}. Current data, however, suggest that the use of AFP does not provide additional benefit to imaging.^{34,39,43}

Staging

Once the diagnosis has been established, the next step is to determine the stage of HCC as treatment options vary depending on the stage of disease. There are multiple staging systems used for HCC, including the American Joint Committee on Cancer (AJCC) TNM system (last revised in 2010), Okuda system, Cancer of the Liver Italian Program (CLIP) score and the Barcelona Clinic Liver Cancer (BCLC) staging classification. Each of these scoring systems have their strengths and limitations.

The Okuda system, developed in 1985, includes tumor size, ascites, bilirubin and albumin to stage patients into three stages (Table 1).⁵⁸ As this system does not include important factors that would alter treatment such as the presence of metastases or vascular involvement, it should not be used to make treatment decisions. It can provide prognostic information for patients however.

The CLIP score includes Child-Pugh stage, tumor morphology (uninodular, multinodular and extension) AFP and portal vein thrombosis.⁵⁹ The CLIP system appears to be the best among the staging systems among patients who underwent transarterial chemoembolization (TACE).⁶⁰ It also appears to be easier and more accurate than the Okuda classification.⁵⁶

The AJCC TNM system was most recently updated in 2010. This system accounts for the size of the tumor, the number of discrete lesions, the presence of vascular

Table 2. Barcelona Liver Cancer (BCLC) Staging Classification

Very Early Stage (0)	1 HCC <2 cm or carcinoma in situ, Child-Pugh A, Okuda 1, PST 0
Early Stage (A)	1 HCC or 3 nodules <3 cm, Child-Pugh A-B, Okuda 1-2, PST 0,
Intermediate Stage (B)	Multinodular HCC, Child-Pugh A-B, Okuda 1-2, PST 0
Advanced Stage (C)	Portal invasion, N1, M1, Child-Pugh A-B, Okuda 1-2, PST 1-2
Terminal Stage (D)	Okuda 3, PST >2, Child-Pugh C

(Llovet, 2004)

involvement, lymph node involvement and the presence of distant metastases.⁶¹ Despite their importance on prognosis, the degree of fibrosis (Ishak classification) does not factor in on the stage.^{62,63} The benefit of the AJCC TNM system is that it (6th edition) has been validated in a cohort of patients who underwent liver transplantation and provided more accurate information regarding overall and recurrence-free survival as compared to six other staging systems, including the CLIP score and BCLC Group staging classification.⁶⁴

The BCLC Group staging classification includes Okuda stage, extent of lesion, performance status, presence of constitutional symptoms, vascular invasion and extrahepatic spread (Table 2).⁶⁵ Because of its ability to stratify patients into groups that would benefit from various treatments, the BCLC is the most commonly used staging system and is the staging system of choice based on the most recent AASLD guidelines.³⁴

Treatment

Treatment options for HCC include surgical resection, liver transplantation, radiofrequency ablation (RFA), trans-arterial chemoembolization, radioembolization and systemic chemotherapeutic agents. The decision regarding the most appropriate therapy for a patient is based on their BCLC stage. The general principle of treatment is that more aggressive measures for earlier stage disease are used with the goal of providing curative therapy. Treatment of more advanced HCC is centered around palliation.

In years past, there were very few patients who were diagnosed with very early stage HCC (BCLC 0, defined as a solitary, asymptomatic lesion with diameter < 2 cm without metastases. Improved surveillance

strategies, adherence to surveillance guidelines and improved diagnostic tools are likely to increase the detection of these very early stage HCCs. Surgical resection is currently recommended for patients with very early stage HCC and Child Pugh A cirrhosis with a bilirubin <1 and no signs of portal hypertension. With surgical resection, the overall 5-year survival is between 70-90%.^{66,67} Even after resection, there is a small risk of recurrence.^{66,67} The presence of satellite lesions is an independent risk factor for survival and recurrence rate.⁶⁶

Randomized controlled trials comparing surgical resection to RFA have shown no survival difference even though lesions were up to 5 cm in size.^{68,69} There are still conflicting data regarding whether or not RFA is a viable replacement for surgical resection in patients with very early stage HCC. A recently published study of 52 patients with very early stage HCC confirmed these findings by showing no difference in 1-, 3- and 5-year overall and tumor-free survival rates when comparing surgical resection and RFA.⁷⁰ However, another study of 237 patients showed that surgical resection provides better overall survival and recurrence-free survival compared to RFA.⁷¹ Given the conflicting data, surgical resection is still the standard of care as the first-line therapy for very early stage HCC.³⁴ If patients with very early stage disease have more advanced liver disease or are otherwise not surgical candidates, either RFA or liver transplantation should be considered.

Early-stage disease (BCLC A) is comprised of asymptomatic patients who are appropriate for resection, liver transplantation or percutaneous treatment.⁷² In patients who are surgical candidates,

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liver transplantation has been proven to be curative.⁷³ In a landmark study by Mazzaferro and colleagues, 48 patients with cirrhosis who had either a single HCC <5 cm or <3 lesions that were less than 3 cm in diameter underwent liver transplantation. There was a 75% 4 year-survival rate and recurrence-free survival was 83%.⁷³ This study became the basis of what is now known as the Milan criteria. In addition to these size restrictions, the Milan criteria also includes the absence of vascular invasion and extrahepatic disease. Overall, the mean survival in patients with early-stage disease who underwent liver transplantation was shown to be 8.8 years, while patients who underwent surgical resection and RFA had a median survival of 4.3 years and 5.2 years, respectively.⁷⁴ Unfortunately, due to the lack of available donor livers, transplantation is not always an option.

Intermediate-stage disease (BCLC B) includes asymptomatic patients with either a large or multinodular HCC and no evidence of vascular invasion or extrahepatic spread.⁷² The current guidelines support trans-arterial chemoembolization (TACE) as first-line therapy for patients in this group who are unresectable.³⁴ This modality can be used as a bridge to liver transplantation as well. Trans-arterial therapy takes advantage of the dependence on the hepatic artery supplying HCC and usually includes a combination of injection a chemotherapeutic agent (suspended in lipiodol to expand exposure of tumor cells to the chemotherapy) followed by embolization of the hepatic artery.³⁴ TACE is contraindicated in patients with vascular invasion due to the increased risk ischemia. A study from 2002 was ended early when it showed that patients who underwent chemoembolization had significant survival benefit as compared to patients who received symptomatic treatment.⁷⁵ In this study, survival probability at 2 years was 63% compared to 27% in the control group. Patients with advanced (i.e., Child C) or decompensated cirrhosis are poor candidates for TACE as liver failure is a potential risk of this treatment.⁷⁶

Advanced stage disease (BCLC C) includes both symptomatic and asymptomatic patients with vascular invasion and/or extrahepatic spread.⁷² End-stage disease consists of patients who are candidates for palliative treatment only because of the poor prognosis.⁷² Patients in either of these stages are candidates only for palliative treatment. Sorafenib is an oral multikinase inhibitor of platelet-derived growth factor receptor. It is a vascular

endothelial growth factor receptor.⁷⁷ Mouse models show that it inhibits tumor growth, vascularization and induces tumor apoptosis and hypoxia.⁷⁸ It has significantly changed the median time to progression of the disease and has prolonged the median survival by almost three months from 7.9 months to 10.7 months.⁷⁷ Patients with Child C cirrhosis with an Okuda score of 3 or an ECOG functional status >2 are defined as a terminal stage (BCLC D) and do not benefit from additional therapy. ■

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