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Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma

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Evidence-based management of patients with hepatocellular carcinoma (HCC) is key to their optimal care. For individuals at risk for HCC, surveillance usually involves ultrasonography (there is controversy over use of biomarkers). A diagnosis of HCC is made based on findings from biopsy or imaging analyses. Molecular markers are not used in diagnosis or determination of prognosis and treatment for patients. The Barcelona Clinic Liver Cancer algorithm is the most widely used staging system. Patients with single liver tumors or as many as 3 nodules ≤3 cm are classified as having very early or early-stage cancer and benefit from resection, transplantation, or ablation. Those with a greater tumor burden, confined to the liver, and who are free of symptoms are considered to have intermediate-stage cancer and can benefit from chemoembolization if they still have preserved liver function. Those with symptoms of HCC and/or vascular invasion and/or extrahepatic cancer are considered to have advanced-stage cancer and could benefit from treatment with the kinase inhibitor sorafenib. Patients with end-stage HCC have advanced liver disease that is not suitable for transplantation and/or have intense symptoms. Studies now aim to identify molecular markers and imaging techniques that can detect patients with HCC at earlier stages and better predict their survival time and response to treatment.

Keywords: Liver Cancer; BCLC; Early Detection; Therapy.

Approximately 700,000 people die of hepatocellular carcinoma (HCC) each year worldwide, making it the third leading cause of cancer death.[1] In the United States and Canada, HCC is the only cancer for which mortality is increasing[2] due to the high prevalence of chronic hepatitis C, immigration from areas where hepatitis B and hepatitis C are common, and the epidemic of nonalcoholic fatty liver disease. The incidence of intrahepatic cholangiocarcinoma might have also increased,[3] but less than 10% of patients with primary liver cancer have this cancer type. In this review, we do not discuss cholangiocarcinoma or the fibrolamellar variant of HCC, which has epidemiological features that differ from those of other HCCs.[4]

Patients with HCC usually present with symptoms of cancer and liver failure unless the cancer is detected at an early stage. Very advanced HCC is untreatable, and most patients die within 3 to 6 months. However, HCC has a prolonged subclinical growth period[5–8] during which interventions can be performed and patients can be cured. We review the evidence to support current methods of surveillance, diagnosis, staging, and treatment of HCC as well as new treatment approaches.

Surveillance of HCC

Identification of Patients at Risk

The most significant risk factor for HCC is cirrhosis. Not all patients with cirrhosis are at equal risk for HCC, and HCC is not always found in patients with cirrhosis. There are no reliable data on the incidence of HCC in patients without cirrhosis. In addition to cirrhosis, other factors associated with increased risk include male sex, older age, persistent increase in alanine aminotransferase level, increased α-fetoprotein (AFP) level, and progressive impairment of liver function.[9] However, knowing that a patient has a risk factor does not aid in the decision of whether to offer surveillance, because risk varies within the population identified by any one risk factor. Increased risk is not sufficient to make surveillance worthwhile; the decision to offer surveillance must also consider the patient's likelihood of receiving treatment if he or she is found to have HCC. If the severity of liver disease and/or comorbidities indicates that effective treatment is impossible, there is no benefit of surveillance.

Guidelines from the American Association for the Study of Liver Diseases (AASLD)[10] were developed on the basis of cost-effectiveness analyses and the risk of HCC in defined populations. More sophisticated models have since produced a number of risk scoring systems[11–21] (Table 1). However, these are not yet ready for general use. Most have not been validated, and many were developed in defined

Abbreviations used in this paper: **AASLD, American Association for the Study of Liver Diseases; AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; c-TACE, conventional transarterial chemoembolization; DEB-TACE, transarterial chemoembolization with drug-eluting beads; HCC, hepatocellular carcinoma; RFA, radiofrequency; RECIST, Response Evaluation Criteria in Solid Tumors; TACE, transarterial chemoembolization.**

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Table 1. Factors That Affect Risk of HCC

Population	Variables	Validation	Reference
Chronic hepatitis B	Age, sex, HBV DNA, cirrhosis, core promoter mutation	No	Yuen et al (GAG-HCC)[11]
Chronic hepatitis B	Age, albumin, bilirubin, HBV DNA, cirrhosis (yes or no)	Variable results in European and North American populations	Wong et al (CU-HCC)[12]
Chronic hepatitis B	Age, albumin, HBV DNA, liver stiffness by transient elastography	No	Wong et al[13]
Chronic hepatitis B	Age, ALT level, HBeAg status, sex, HBV DNA	Yes (only in Asia)	Yang et al (REACH-B)[14]
Chronic hepatitis B	Age, sex, ALT level, HBV DNA, quantitative HBsAg, HBV genotype, HBeAg status	No	Lee et al[15]
Chronic hepatitis C F3 and F4	Age, race, alkaline phosphatase level, esophageal varices, smoking, platelet count	No	Lok et al[16]
Hepatitis C cirrhosis	ALT level, AFP level, age, platelet count	No	El-Serag et al[17]
Liver transplant waiting list	Age, diabetes, race, etiology of liver disease, sex, severity (CTP score)	Yes	Flemming et al (ADRESS-HCC)[18]
General population	Age, sex, ALT level, liver disease, family history of HCC, cumulative smoking history	No	Hung et al[19]
General population	Age, sex, alcohol consumption, body mass index, diabetes (yes or no), coffee consumption, hepatitis B, hepatitis C	No	Michikawa et al[20]
HCV post SVR	Age, sex, platelet count, AFP level, fibrosis stage, HCV genotype	No	Chang et al[21]

ALT, alanine aminotransferase; CTP, Child-Turcotte-Pugh; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HCV, hepatitis C virus; SVR, sustained virologic response.

populations. Only one report has translated degree of risk into a decision of whether or not to provide surveillance.[19] Other studies presume that patients at highest risk require surveillance; however, among those with lower levels of risk, there is no reliable cutoff value below which surveillance is unnecessary. Finally, risk scoring systems were all developed in untreated populations and may not perform equally well in treated patients.

Liver stiffness has also been used to predict risk of HCC, either individually or in combination with a risk score,[22–24] but a threshold for institution of surveillance has not been adequately defined. The AASLD criteria for surveillance are very broad; in the absence of a defined risk threshold, it is probably wise to err on the side of being more inclusive and apply the AASLD incidence cutoff of 1.5% – 2% for patients with cirrhosis and 0.2% for patients with chronic hepatitis B.

Evidence to Support Surveillance and Its Methodology

Surveillance of HCC is controversial.[25] The evidence to support surveillance primarily comprises demonstration of stage migration and more frequent application of potential curative treatment in screened populations. There have been 2 randomized trials of HCC surveillance, and both were performed in China.[26,27] One used AFP level at screening,[26] and the other used AFP level plus findings on ultrasonography.[27] The first study failed to show a benefit of surveillance. The second study found a 37% reduction in mortality with surveillance, but this study has been heavily criticized. Nonetheless, in balancing potential benefit versus potential harm, the equation clearly tilts toward surveillance. The most impressive data from a prospective study that supported surveillance came from an analysis of a Taiwanese population in which subjects were selected for surveillance based on a risk score.[28] Mortality in the group that received surveillance was reduced compared with the control group and the general population. Virtually all cost-effectiveness analyses of surveillance find it to be effective and cost-effective according to accepted definitions.[29–36]

Patients with HCC identified by surveillance present with smaller tumors and are more likely to undergo a curative procedure.[37–39] These cohort studies are subject to lead time and length bias, which cannot be completely avoided[40] (Figure 1). A recent meta-analysis[41] concluded that despite poor-quality evidence, HCC surveillance increased the life expectancy of patients with cirrhosis.[41] However, a systematic review concluded that there was insufficient evidence to recommend surveillance.[42] Because clinicians who care for patients with liver disease all too often see unscreened patients presenting with advanced HCC, an a priori argument can be made that patients at risk should undergo surveillance, at least until there is evidence that surveillance is inefficient.

Ultrasonography is the recommended method of surveillance for HCC.[9,10,43] There is controversy over use of assays that measure levels of AFP, des-γ-carboxy prothrombin,