Screening for Hepatocellular Carcinoma: What Is Missing?

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While there are guidelines from all major liver societies for the screening and management of hepatocellular carcinoma (HCC), many issues remain surrounding the actual practice of screening. This review discusses how to diagnose and screen HCC and more importantly, how well we diagnose and screen for HCC. Improved survival and outcomes after HCC diagnosis depend upon accurate diagnosis of cirrhosis and the timeliness of screening. With all oral direct-acting antivirals now widely available for hepatitis C, there are increasing numbers of patients who may be cured but are still at risk of HCC. Some uncontrolled studies suggest that direct-acting antiviral therapy may even increase the risk of HCC. Before we discuss expansion of who should be screened, we need physicians to realize how poorly we screen those patients who are already recommended for screening by guidelines. (HEPATOLOGY COMMUNICATIONS 2017;1:18-22)

How big is the problem?

The last four decades has seen a rising incidence of hepatocellular carcinoma (HCC) in the United States from 1.5 per 100,000 persons to nearly 14 per 100,000 persons and a 5-year survival under 12%.[1] While most of the increase is associated with aging of the baby-boomer population with hepatitis C, hepatitis B and nonalcoholic fatty liver disease also contribute. In a Markov model of 2.7 million persons infected with the hepatitis C virus (HCV) who are in primary care in the United States, it is estimated that 1.47 million will develop cirrhosis and 350,000 will develop liver cancer over their lifetime. The burden of HCC from HCV is estimated to peak at 12,000 per year by approximately 2030.[2]

Who should be screened

Surveillance is the process of providing a screening test at regular intervals to patients at risk for HCC. Surveillance is deemed cost-effective if the expected HCC risk exceeds 1.5% per year in patients with hepatitis C and 0.2% per year in patients with hepatitis B.[3] All patients with cirrhosis should be screened. While it is possible to perform HCC risk stratification in these patients using clinical risk scores[4,5] and genomic biomarkers,[6] neither yet appear able to reliably identify those patients with cirrhosis who are at such a low risk of HCC development that screening is not warranted. In addition to screening all patients with cirrhosis, hepatitis B virus (HBV) Asian males ≥ 40 years, Asian females ≥ 50 years, and sub-Saharan Africans ≥ 20 years as well as HBV patients with a family history of HCC should be screened. The European Association for the Study of the Liver (EASL) recommends screening HCV patients with stage 3 fibrosis as well.[7] One of the major problems in deciding who to screen is in identifying those patients who have cirrhosis.[8] If patients are decompensated with ascites, jaundice, encephalopathy, splenomegaly, and muscle wasting, the diagnosis is relatively easy. However, in some patients with Child's A

Abbreviations: AFP, alpha-fetoprotein; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CT, computed tomography; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MRI, magnetic resonance imaging; SVR, sustained virologic response; VHA, Veterans Health Administration.

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cirrhosis, few signs may be noted, and many such patients have normal liver tests. With decreasing use of liver biopsy, noninvasive markers of fibrosis may miss many patients. Transient elastography can be used to stage fibrosis in a noninvasive manner by measuring shear wave velocity. This technique is not readily available throughout the United States at this time so patients with cirrhosis may not be appropriately diagnosed.

How to screen

Screening is recommended by all liver societies; 6-monthly ultrasounds are recommended by the EASL and American Association for the Study of Liver Diseases[7,9] and ultrasound and alpha-fetoprotein (AFP) are recommended by the Asian Pacific Association for the Study of the Liver.[10] Screening every 6 months is recommended because the doubling time of HCC is estimated to be 4-6 months.[11] The only randomized controlled trial of screening versus no screening was in 18,816 hepatitis B patients in China.[12] Patients underwent AFP and ultrasound every 6 months; 58.2% were screened and 41.8% were not. There were 86 tumors in the screened patients and 67 tumors in the nonscreened patients. Only the screened patients had subclinical, small, or resectable HCC lesions (Table 1). Survival was markedly better in those who were screened versus those who were not (65.9% versus 31.2% at 1 year; 46.4% versus 0% at 5 years).

AFP is limited as a screening test because of both false positives and false negatives. A third (20%-40%) of patients with HCC have normal AFP, and 20%-30% of patients without HCC have abnormal AFP, especially in those with active inflammation and elevated alanine aminotransferase (ALT) from HCV[5] and HBV.[13] Analyzing nearly 12,000 HCV patients with cirrhosis in the Veterans Health Administration (VHA) system, an AFP-based algorithm was created that also included ALT, platelet count, and age to predict the development of HCC.[5] The authors found that taken alone, a patient with an AFP of 120 ng/mL had an 11% probability of developing HCC within 6 months; however, if that same patient was known to have minimal liver inflammation (ALT 40), platelet count of 100, and be older (age 70), the probability of developing HCC within 6 months rose to 29%. While AFP is not a particularly sensitive screening test and should be considered alongside additional clinical factors, such as ALT, there is no doubt that the higher the AFP, the more likely the diagnosis is HCC. In addition, AFP can be used as a prognostic marker because it predicts overall mortality in HCC,[14] predicts prognosis after resection,[15] and predicts prognosis after liver transplantation.[16-19]

If a nodule >1 cm is found on ultrasound, quadruple-phase computed tomography (CT) or magnetic resonance imaging (MRI) is recommended.[3] Quadruple-phase CT is used to differentiate HCC, which is usually supplied by the hepatic artery, from normal liver tissue, which is mainly supplied by the portal vein. HCC is characterized by arterial phase enhancement and portal venous washout at the time the majority of the liver is enhanced. If either the CT or MRI shows the typical characteristics of HCC, then patients should be managed as per regular guidelines (e.g., Barcelona Clinic Liver Cancer [BCLC] staging classification[20]), without biopsy diagnosis. Biopsy of the lesion is recommended only in selected cases if there is an atypical radiologic appearance; this is because there are concerns with liver biopsy. False negative biopsies are common in clinical practice and may lead to delays in both diagnosis and treatment.[21] Tumor seeding along the biopsy tract occurs in 1%-5% of cases, but coaxial biopsy may decrease this rate.[22] Seeding may exclude the patient from consideration of curative treatments, such as resection or transplant. If radiologic appearance and biopsy results are nondiagnostic or if the lesion is <1 cm, short-term follow-up with ultrasound (or CT/MRI if patient is listed for a transplant) in 3-4 months is recommended to assess growth of the lesion.

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TABLE 1. Efficacy of Screening for HCC in Patients with Cirrhosis

	Ultrasound Surveillance Interval								
	Every 6 Months			Every 12 Months			No Screening		
Study Design 1st Author(Ref)	n	Within Milan (% treatable)	Survival (% or median)	n	Within Milan (% treatable)	Survival (% or median)	n	Within Milan (% treatable)	Survival (% or median)
Retrospective Stravitz[24]	172	70%	3 yr: 39%	48	37%	3 yr: 27%	59	7%	3 yr: 12%
Retrospective Trevisani[25]	215	69%	36 mos	155	60%	34 mos	451	31%	14 mos
Prospective Santi[26]	510	70% (82%)	45 mos	139	58%* (70%)	30 mos†	Not studied		
Prospective Zhang[12]	86‡	45% (79%)	1 yr: 66% 5 yr: 46%	Not studied			67‡	0% (49%)	1 yr: 31% 5 yr: 0%

*Compared to every 6-month screening *$P < 0.001$;
†$P = 0.03$.
‡Total n included in study was 9,373 in every 6-month arm and 9,443 in no screening arm.

Singal studied 446 patients with cirrhosis who were prospectively enrolled for 6-monthly ultrasound and AFP.[23] They excluded the first 6 months to avoid lead-time bias. After a median of 3.5 years, 41 patients were identified with HCC, 73.2% of whom had early lesions (BCLC stage 0-B) with the same percentage within Milan criteria and 80.5% within University of California, San Francisco criteria. They found an annual HCC incidence of 2.8% and a cumulative incidence at 3 and 5 years of 5.7% and 9.1%, respectively. The sensitivity of AFP and ultrasound was 90%, which was greater than either alone. However, screening came at a cost: 36 patients with high AFP had normal MRI and CT and 34 patients had a lesion on ultrasound that was not identified from MRI or CT.

Another retrospective study compared 6-monthly and yearly ultrasounds versus no screening in 269 patients with cirrhosis and HCC (Table 1).[24] Those HCC patients who had appropriate screening had smaller lesions (70% within Milan criteria) compared to 37% for those screened yearly and 7% who had no screening. In addition, 3-year survival was better in 6-monthly (39%) screening versus yearly (27%) or no screening (12%). Among 821 Italian HCC patients who were studied retrospectively, no difference was found between 6- and 12-monthly screening compared to no screening.[25] However, a later prospective study from the same group confirmed the benefit of 6-monthly screening over 12-monthly screening in 649 Italian patients with cirrhosis.[26] As shown in Table 1, in those patients with 6-monthly screening, 70% were within Milan criteria compared to 58% of those screened yearly being within Milan criteria ($P < 0.001$). Screening more frequently (3 versus 6 months) increased detection of small focal lesions but not of HCC.[27] Systematic reviews and meta-analysis of surveillance studies in patients with cirrhosis showed that those who had routine screening usually had earlier stage HCC, were more likely to be candidates for curative treatment, and had better survival compared to unscreened patients.[28,29]

How well do we screen?

Studies from Europe and the United States show that less than 30% of patients with cirrhosis receive screening. In one study of 904 patients with cirrhosis in a US safety net hospital, less than 2% had biannual ultrasounds, 13% had annual ultrasounds, and 67% had only one ultrasound in 3 years.[30] Lower surveillance was noted in the uninsured patients and in African Americans. Surveillance was highest in those who had a yearly visit to a hepatologist, followed by a visit to a primary care doctor; both were better than no follow-up visit.[30] Two large, recent, retrospective studies of patients in the VHA[31] and with commercial insurance[32] found that twice yearly ultrasound screening in patients with cirrhosis was performed 20%-30% of the time. In the VHA study, some of the strongest predictors of not receiving screening included fewer visits with a subspecialist (gastrointestinal/hepatology/infectious disease), increased distance from a patient's home to the nearest VHA center, and a longer time between the date the ultrasound was ordered and the date it was requested to be performed.

Screening of HCV patients after cure

Treatment of hepatitis C markedly decreases the risk of HCC but does not eradicate it. To emphasize

this, a study of 33,000 VHA patients identified 10,827 patients who achieved sustained virologic response (SVR) with interferon-based therapies; of those who achieved SVR, 100 developed new HCC.[33] The annual incidence rate of HCC in those with SVR was 0.33% per year compared to 1.32% per year in those without SVR. The predictors of developing HCC in this cohort were cirrhosis at SVR (odds ratio, 6.69; confidence interval, 4.3-10.4), age over 65 years (4.51; 2.0-10.4), age 55-64 years (2.04; 1.3-3.2), Hispanic race compared to Caucasians (2.3; 1.1-1.8), diabetes mellitus (1.8; 1.2-2.9), and alcohol (1.68; 1.08-2.6).

Thus, patients who have SVR or are cured of their hepatitis C are still at risk of developing HCC, need to be monitored, and should not be discharged from their doctor's practice. Literature over the past year has noted HCC occurring or recurring after SVR in response to direct acting antivirals. Uncontrolled studies reported early recurrence within 6-12 months of SVR,[34,35] but the Agence Nationale de Recherche sur le Sida reported no difference in HCC incidence in those treated with interferon-based therapies versus direct-acting antivirals.[36] Whether all oral direct-acting antiviral therapy is associated with an increased risk of cancer is not clear, and further long-term randomized studies are required.

In summary, there is an increasing prevalence of HCC with the aging of patients with hepatitis C, the increase of nonalcoholic fatty liver disease, as well as hepatitis B. There is much discussion about screening patients without cirrhosis as these patients can develop HCC. However, this opinion piece highlights that the major problem worldwide is how poorly we appropriately screen and diagnose HCC in patients with cirrhosis. What is most important is to diagnose cirrhosis early so that screening can be initiated because patients with cirrhosis are those with the highest risk of HCC. The outcome of HCC is influenced by the failure to diagnose cirrhosis, the absence of surveillance, and the delay in follow-up and treatment. Screening appropriately leads to early diagnosis, which leads to better management options, a higher proportion of treatable lesions, and better outcomes, including survival.

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