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Screening for Hepatocellular Carcinoma: Who, What, When, and Why

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Hepatocellular carcinoma (HCC) is one of the fastest growing causes of cancer worldwide. Two interventions are proven to improve HCC outcomes: early detection of HCC and treating the underlying cause of liver disease. In this review, we present best practices for HCC screening and evaluation. We highlight patient selection (namely patients with hepatitis B virus infection and anyone with cirrhosis), modality (ultrasound with alfa-fetoprotein with mention of alternatives), and the ideal sequence of events for patients from diagnosis to curative therapy.

INTRODUCTION

Hepatocellular carcinoma (HCC) is a growing public health threat.[1] Its global incidence has increased rapidly with incidence rates expected to climb further particularly among Black and Hispanic persons.[2] The median survival of HCC is 11 months, however morbidity and mortality vary by stage of disease and management strategies.[3] Crucially, less than half of HCC is discovered at an early stage, reducing the possibility of curative therapy.[4] While there are limited randomized controlled trials on HCC screening, existing studies have shown HCC detection and subsequent curative therapy is significantly increased in patients undergoing screening with ultrasound and serum biomarkers, than those not screened.[5] This review aims to describe the at-risk populations and mechanisms for HCC screening in accordance with the American Association for the Study of Liver Diseases guidelines.

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Epidemiology

Cirrhosis is the primary risk factor for HCC, accounting for 80-90% of HCC with an annual incidence of 2-4%.[6,7] HCC is more common among men and older persons.[8] The highest incidence is

among people with uncured/viremic hepatitis C and uncontrolled hepatitis B infections.[9,10] Globally, however, Asia and sub-Saharan Africa still comprise the majority of HCC due to endemic Hepatitis B infection (HBV), a major risk factor for HCC.[11] Concurrently, the rising tide of nonalcoholic fatty liver disease (NAFLD), considered the hepatic component of metabolic syndrome, has eclipsed hepatitis C in its contribution to the burden of HCC.

Prevention of HCC

HCC prevention is limited to prevention of chronic liver disease in general, including HBV vaccination. Much like cervical cancer, HCC can arise from an oncogenic viral infection. In areas where HBV is endemic, approximately 70% of HCC patients test positive for hepatitis B surface antigen (HBsAg).[12] HCC in children is generally the result of perinatal transmission.[13] The HBV vaccine has reduced transmission. The United States adopted a universal HBV infant vaccination policy in 1991 including testing of all pregnant patients for HBsAg and prophylaxis for their infants, infant vaccination, and vaccination of adults in high risk groups.[14] While this program hasn't been optimally implemented in America, evaluation of universal childhood HBV vaccination programs in countries like Taiwan show a significant reduction in HCC in postvaccine birth cohorts compared to prevaccine cohorts.[15]

HBV Treatment

In general, therapeutic control of HBV can both reduce but not eliminate the risk of HCC.[16] A large RCT from Taiwan assigned patients with HBV-related cirrhosis or advanced fibrosis to receive lamivudine or placebo to evaluate liver disease progression, including HCC. While the study was terminated early due to major differences between the treatment and placebo group, HCC was noted to occur in significantly fewer patients in the lamivudine group (3.4%) compared to those receiving placebo (8.8%).[17]

Hepatitis C Treatment

Cure, or sustained virologic response (SVR), of hepatitis C is associated with a lower risk HCC. HCV eradication also reduces the risk of HCC,[18,19] but the risk of HCC can remain elevated, particular among older persons with low platelets or albumin, high liver stiffness or Fibrosis-4 indices, and those who are actively drinking alcohol.[18,20]

Lifestyle Considerations

There is limited data regarding diet and lifestyle interventions for HCC risk. A number can be inferred, however, from observational data. A study using the Surveillance, Epidemiology, and End Results (SEER) database found the population attributable fraction of diabetes and obesity (hallmarks of NAFLD), to have a 37% contribution to HCC development.[21] As metabolic syndrome is a pro-carcinogenic state, targeting metabolic risk factors may be an important part in HCC risk mitigation.

Use of greater than 80g of alcohol per day can increase risk of HCC nearly 5-fold.[22] Alcohol is a multiplier of risk, even for persons with viral hepatitis.[23]

Why Screen for HCC?

Early HCC diagnosis remains difficult for many reasons. There are neither symptoms nor physical exam findings early in the disease course specific to HCC. Liver enzyme or function testing is similarly inadequate.[24] Symptomatic disease is often locally advanced or metastatic with few therapeutic options that have limited efficacy, despite recent advances in systemic HCC therapeutics. Whereas patients detected at late stages have a median survival less than one year, patients detected at an early stage can undergo curative therapy and achieve 5-year survival exceeding 70%.[4,25] Early stage HCC can be cured through ablation, surgical resection, or liver transplantation. Given that late-stage HCC is associated with reduced survival, poor quality of life, and can only be treated with expensive systemic therapies, efforts to identify early-stage HCC are cost-effective.[26]

As the principal risk factors for HCC are identifiable – cirrhosis and hepatitis B – screening can be targeted towards those most likely to benefit. Competing risks, such as life-limiting comorbidities and frailty, may play a role in deciding to enroll a patient in a screening. Among those with HBV, men >40 years old, females >50 years old, and those with a family history of HCC should be screened.[27]

Table 1. Screening and Diagnosis for HCC

	Recommendation
Population to Screen	Child Pugh A or B cirrhosis of any etiology
	Child C cirrhosis on the liver transplant waitlist
	HBV infected patients > 40 years of age, females > 50 years of age, and those with a family history of HCC
Screening Interval	Every 6 months (range 4-8 months)
Screening Imaging Modality	Ultrasound
	Contrast-enhanced cross-sectional imaging if nodular liver or poor quality ultrasound
Biomarkers	Alpha-Fetoprotein (AFP)
Lesion Size Criteria	> 1 cm should trigger diagnostic imaging
AFP Criteria	> 20 ng/mL should trigger diagnostic imaging
Diagnostic Imaging Modality	Multiphase CT or MRI
Liver Biopsy	Not routine
Diagnosis Follow-up	LI-RADS 1-2 – return to ultrasound screening
	LI-RADS 3 – obtain MRI in 3-6 months
	LI-RADS 4 – multidisciplinary discussion, consider follow up imaging < 3 months
	LI-RADS 5 – confirmed HCC

CT = computed tomography, HCC = hepatocellular carcinoma

How to Screen? (Table 1.)

First, while many patients with cirrhosis have subspecialists who assume responsibility, most do not. In evaluation of primary care physician (PCP) practices, a recent survey study demonstrated nearly a third of PCPs defer HCC screening to subspecialists.[28] Effective cancer screening is a balance of accuracy of the test, ease of utilization, and cost effectiveness. Early screening algorithms proposed screening with alpha-fetoprotein (AFP). However, limitations with AFP soon became obvious, including serum elevations in the absence of HCC, remaining normal in setting of HCC, and inability for AFP to necessarily detect early stage tumors.[29] A seminal study by Sheu et al. noted normal AFP in nearly half of patients presenting with hepatomas less than 5cm, which would have otherwise been missed.[30] Ultrasound (US) was later introduced as a cost effective imaging modality for screening; the first RCT for HCC screening with US and AFP showed close to 40% reduction in HCC associated mortality compared to those with no screening, with a mortality rate ratio of 0.63 (95% CI 0.41, 0.98) with a 58% adherence rate. Given limitations of AFP alone, the AASLD recommends using ultrasound (with or without AFP) every 6 months. Computerized tomography (CT) and magnetic resonance imaging (MRI) have been investigated mainly as diagnostic modalities for HCC, and data for their use in HCC screening are limited. Not only are CT and MRI more costly than US, but radiation exposure and availability, respectively, have precluded their inclusion in national guidelines. However, they may be considered for screening in patients with central obesity or hepatic parenchymal heterogeneity secondary to cirrhosis.[27] Recently, some centers have adopted 'abbreviated MRI' as a way of screening for HCC using contrast-enhanced sequences with data suggesting high sensitivity and patient acceptability.[31] Finally, there are emerging data regarding novel blood-based biomarkers for screening but these are not ready for practice implementation.

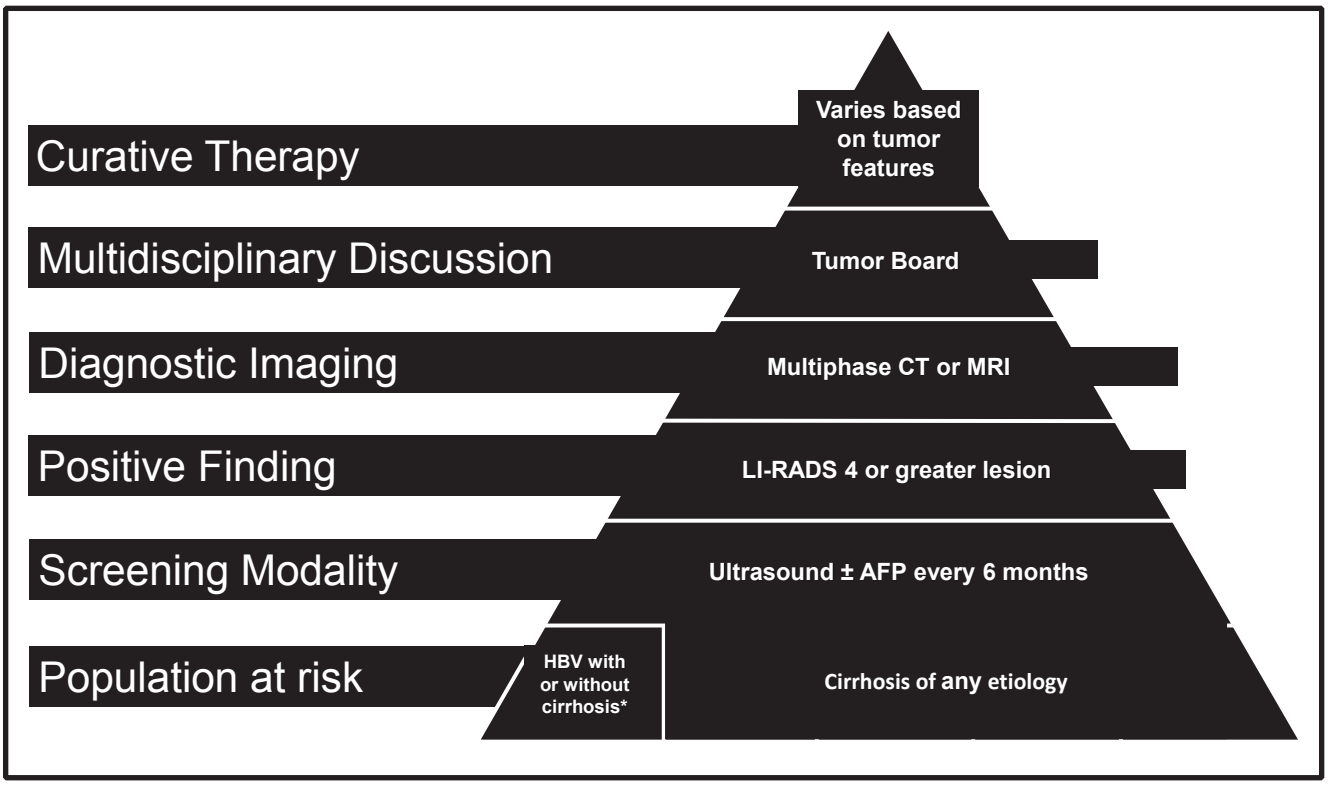

Figure 1. Ideal Scenario for HCC Screening

A patient from a population at risk is identified, and undergoes liver ultrasound (US) with or without serum alpha-feto protein (AFP) every six months. A nodule (> 10mm) is found on imaging (or AFP > 20ng/mL) and cross sectional imaging is obtained with either a multiphase computerized tomography (CT) or magnetic resonance imaging (MRI). The nodule is classified as a LI-RADS 4 or greater and a tumor board containing experts from multiple disciplines (hepatologist, hepatobiliary/transplant surgeon, interventional radiologist, radiation oncologist, medical oncologist, etc.) discusses the optimal treatment strategy. Depending on the characteristics of the lesion, the patient's comorbidities, and functional status, a variety of curative therapy options can be pursued (surgical resection, locoregional therapy, systemic therapy, and/or liver transplantation).

What to do When I Find Something? (Figure 1.)

Prompt diagnostic evaluation is the cornerstone of HCC screening effectiveness, as tumor stage at diagnosis is the single strongest prognostic indicator.[4] Unlike many other cancers, HCC diagnosis can be established with imaging without definitive need for biopsy. However, not all nodules seen by ultrasound are HCC. When a suspicious lesion is found, patients should undergo cross-sectional diagnostic imaging with a multiphasic CT or MRI. Owing to the differential blood supply of the liver (primarily portal veinous blood) and HCC (primary arterial), the timing of contrast phase can identify lesions as HCC or not. Liver lesions are categorized and interpreted according to the American College of Radiology criteria for Liver Imaging Reporting and data system (LI-RADS).[32] Lesions are classified from definitely benign (LI-RADS 1) to definitely HCC (LI-RADS 5), as well as non-HCC malignancy (LI-RADS M) and noncategorizable (LI-RADS NC). For LI-RADS 4 lesions and above, the AASLD recommends a multidisciplinary discussion, with biopsy in select cases, or follow up imaging in 3 months. Treatment options for HCC include curative therapies such as surgical resection, locoregional therapy (ablation or radiation), palliative therapies (chemoembolization, radioembolization), or organ transplantation. Each stage of the evaluation from diagnosis to selection

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of treatment options to follow-up benefits from the coordination of a multidisciplinary team.

CONCLUSION

HCC is increasingly common and the best available tool to reduce its morbidity and mortality is screening. Screening should be performed for patients with cirrhosis and/or hepatitis B. At this time, best practice includes semi-annual ultrasound and AFP. Nodules should be evaluated using multiphasic cross-sectional imaging. Diagnosed HCC should be evaluated by multidisciplinary clinics. ■

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