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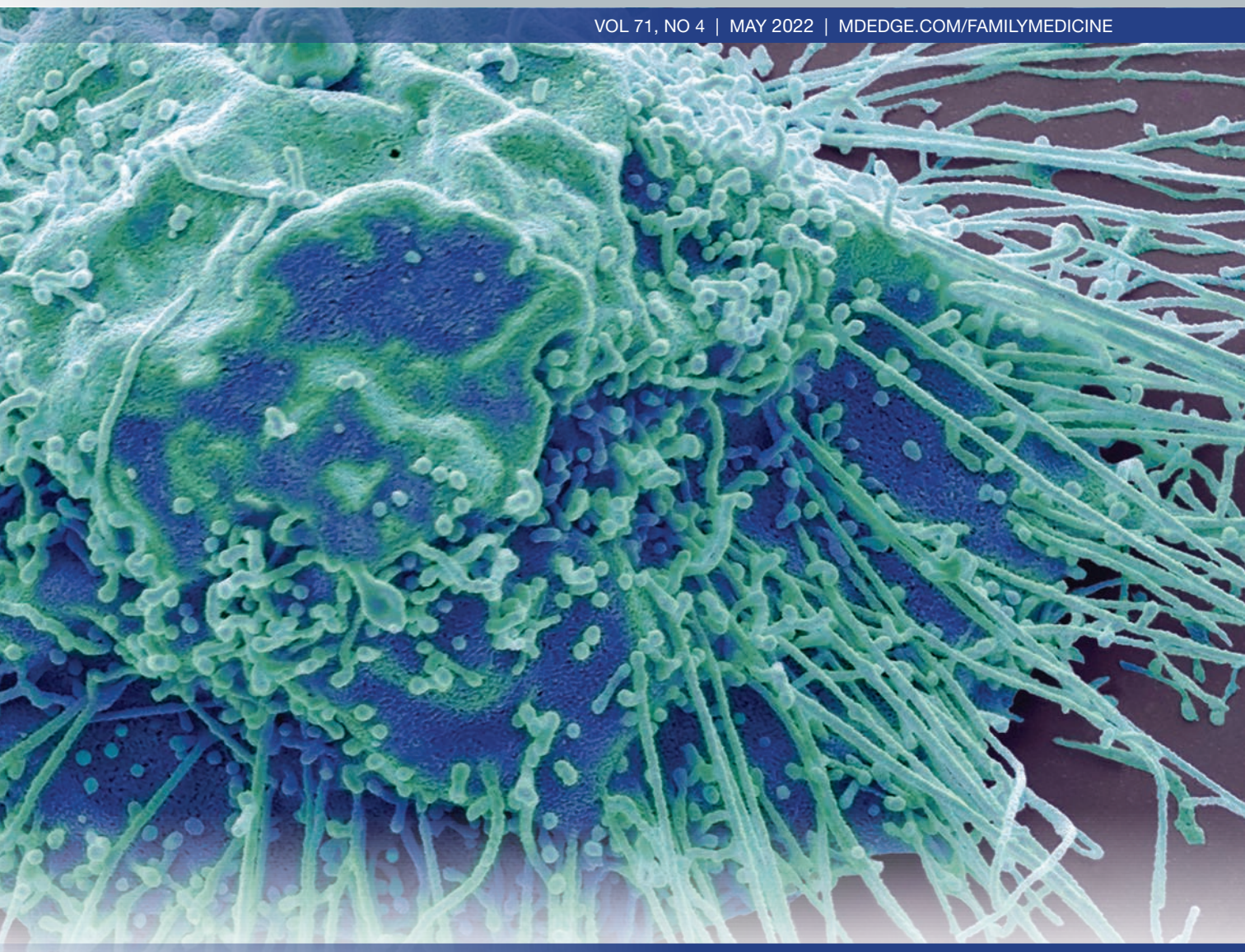

Optimizing the Suboptimal: Hepatocellular Carcinoma Surveillance Guide for Primary Care Practitioners

Based on a Medscape Education Online Activity

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GOAL STATEMENT

The goal of this activity is to update primary care practitioners (PCPs) on risk factors and trends in hepatocellular carcinoma (HCC) development, as well as guideline recommendations and best practices for collaborating with specialists in HCC surveillance.

LEARNING OBJECTIVES

After participating in the activity, healthcare providers will have:

Increased knowledge regarding the
- Epidemiologic patterns associated with HCC
- Risk factors for developing HCC
- Guidelines for HCC surveillance

Greater confidence in their ability to
- Incorporate surveillance guidelines into practice
- Differentiate the roles of PCPs and specialists in HCC surveillance

TARGET AUDIENCE

This activity is intended for primary care physicians, nurse practitioners (NPs), physician assistants (PAs), and other clinicians involved in the care of patients at risk of liver cancer.

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HEPATOCELLULAR CARCINOMA: A LOOK AT EPIDEMIOLOGIC PATTERNS

Hepatocellular carcinoma (HCC) is the most common type of liver cancer, representing the sixth most commonly diagnosed cancer and third leading cause of cancer-related death worldwide.[1,2] Specifically in the United States, over 42,000 patients were diagnosed with HCC in 2021 and this aggressive malignancy was associated with over 30,000 deaths, making it the sixth leading cause of cancer-related death.[3] In the United States, the rates of HCC incidence and mortality have continued to increase over the last several decades, although the number of new cases appears to have declined slightly in the last few years.[4]

While screening programs for patients with liver cirrhosis have improved identification of HCC, many patients are still diagnosed with advanced stage disease, which is associated with a poor prognosis. The 5-year relative survival rate for all patients with HCC or intrahepatic bile duct cancer (the other primary cancer of the liver) is 20.3%, but drops to only 12.3% for those with regional lymph node involvement and 2.7% for patients with distant metastases.[4] The mortality associated with HCC is often influenced not only by the disease itself, but also by underlying liver cirrhosis and related complications, which can hamper both diagnosis and treatment of HCC.[1]

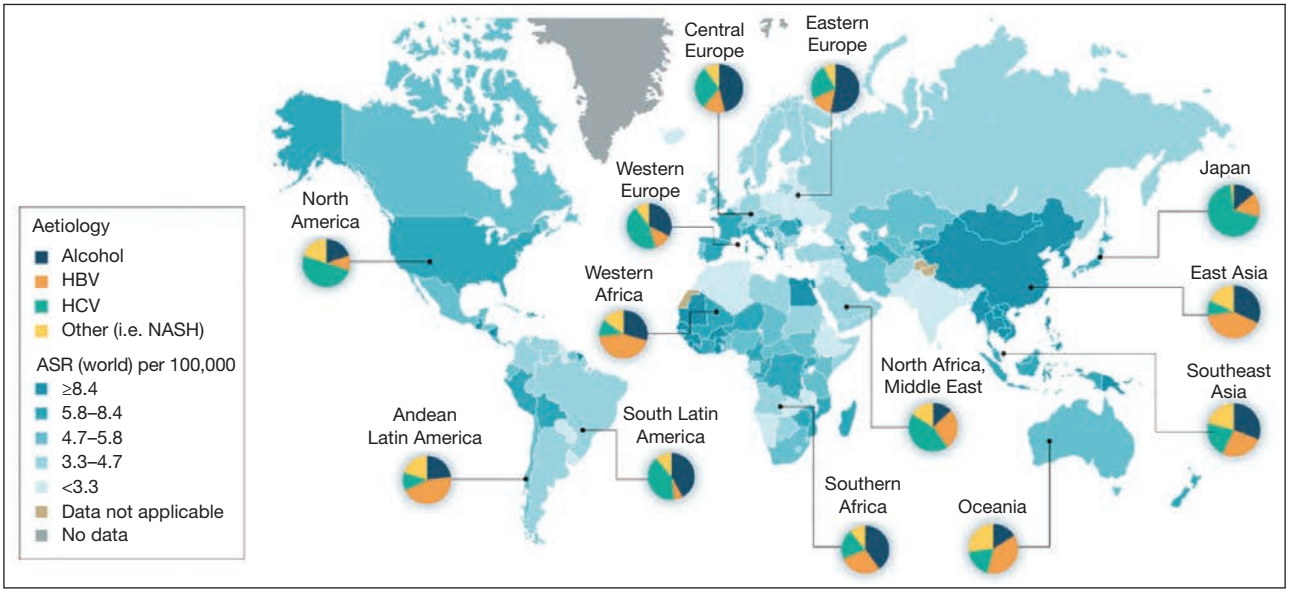
HCC is more common among males, with a male to female ratio exceeding 2.5 for both incidence and mortality.[3] This distribution is presumably related to multiple factors, including increased prevalence of specific risk factors in males such as alcohol consumption and tobacco use.[5] There are also epidemiologic differences in HCC incidence and mortality across different races and ethnicities within the United States. The highest rates of HCC are observed in patients of Asian and Pacific Islander background, as well as Hispanic patients. HCC-related mortality is higher among Black and Hispanic patients compared with White patients, which may reflect differences in the prevalence of different risk factors and potential differences in access to care.[6] For instance, Black and Hispanic patients are more likely to have HCC diagnosed when it is already at an advanced stage and are also less likely to undergo curative treatment.[7]

Global geographic variations in the rate of HCC are reflective of the heterogeneous distribution of risk factors, including hepatitis B virus (HBV), hepatitis C virus (HCV), alcohol consumption, and obesity (**FIGURE 1**).[1] The highest incidence of HCC worldwide is in East Asia and West Africa, although North America, Western Europe, and Australia also have a relatively high incidence.[8] Within the US, the western and southern states appear to have a higher incidence of HCC compared with other regions.[6] Continued evolution in the epidemiology of HCC is expected due to population growth and aging, as well as increased utilization of HCC screening and HBV vaccination programs.[5]

IDENTIFYING THOSE MOST AT RISK FOR HCC

Major risk factors for development of HCC include HBV and HCV infection, alcohol consumption, and obe-

FIGURE 1. **Incidence of HCC Based on Geographical Region and Etiology[1]**



Legend: ASR, age-standardized incidence rate; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis.

Source: Reprinted by permission from Springer Nature: *Nat Rev Dis Primers*. Hepatocellular carcinoma, Llovet JM, Kelley RK, Villanueva A, et al., 2021.

sity- or diabetes-related nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). Although these factors vary widely, they share a common propensity for driving chronic inflammation and persistent liver injury, promoting and exacerbating hepatic malignancy related to oxidative stress, immune dysregulation, and interactions with the microenvironment.[1] Approximately 90% of all HCC cases occur in patients with underlying liver cirrhosis, with approximately one-third of patients with liver cirrhosis anticipated to eventually develop HCC.[1,5] Other less-common risk factors include aflatoxin exposure, tobacco use, hemochromatosis, porphyria, and other metabolic disorders.[9] Older age and male sex also increase an individual's risk for HCC.[1,4]

The relative contribution of different etiologies to the development of HCC varies markedly by geographical region (**FIGURE 1**). HBV infection is the most common cause of HCC worldwide, accounting for approximately 30% to 45% of cases in western and southern sub-Saharan Africa and approximately 40% throughout east Asia.[5] In contrast, only 9% of HCC cases were attributed to HBV infection in North America.[5] HCV infection appears to be the predominant etiology for HCC in the Asia-Pacific region, north Africa, and western Europe.[5] Increasing uptake of HBV vaccination and successful antiviral treatment of HCV continues to reduce the incidence of these viral infections and will hopefully reduce HCC incidence in the coming years.[1]

In the United States, HCV infection and alcohol use are the 2 most common risk factors for HCC, although the role for NASH in tumorigenesis is increasing.[1,5] Surveillance data from 2015 showed that approximately 37% of HCC cases in North America were attributed to alcohol-related cirrhosis.[5] Alcohol use is also a major risk factor in central and eastern Europe and southern Latin America (**FIGURE 1**).[1]

The HCC risk factors NAFLD and NASH are associated with obesity and diabetes mellitus and can lead to subsequent liver malignancy in the presence or absence of liver cirrhosis. While the annual incidence of NASH-related HCC is relatively low (approximately 1% to 2% per year),[10] it is estimated that 15% to 20% of all HCCs can be attributed to NASH.[11] The role of NASH as a driving factor in the development of HCC will likely grow with the increasing rate of obesity and diabetes in the United States and other developed countries.[1,12] Obesity is also associated with poorer outcomes in patients with HCC, with an increased relative risk of death in those with a higher body mass index (BMI).[13]

Careful assessment of a patient's unique set of risk factors can help primary care physicians, gastroenterologists, and hepatologists make decisions regarding HCC screening.[14] The importance of liver cirrhosis as an etiological factor for HCC reinforces the importance of accurate assessment of liver function. One of the ways liver function is assessed in the clinical setting is using the Child-Pugh classification (**TABLE 1**). Five factors contribute to the score: bilirubin level, albumin level, inter-

TABLE 1. **Child-Pugh Scoring System**[15]

Criteria	Points		
	1	2	3
Bilirubin (mg/dL)	< 2	2 to 3	> 3
Albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
INR	< 1.7	1.7 to 2.3	> 2.3
Ascites	None	Slight	Moderate
Encephalopathy (grade)	None	1 to 2	3 to 4
Classification	**Points**		
A	5 to 6 (good risk, least severe)		
B	7 to 9 (moderate risk, moderately severe)		
C	10 to 15 (poor risk, most severe)		

Source: Reproduced from National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology. Hepatobiliary Cancers. Version 5.2021. Published September 21, 2021. Accessed December 10, 2021. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf

national normalized ratio (INR), presence and degree of ascites, and presence and degree of encephalopathy. The Child-Pugh score can assist the healthcare team in determining the severity of a patient's liver impairment related to cirrhosis or other factors, which can help identify those who should be screened for HCC and how patients diagnosed with HCC should be treated.[15]

UNDERSTANDING CURRENT HCC SURVEILLANCE GUIDELINES

Screening programs have demonstrated significant benefit for the early detection of a number of tumor types, including cancers of the breast, colon, prostate, and cervix.[16] The reality that 80% to 90% of patients with HCC have pre-existing chronic liver disease creates the

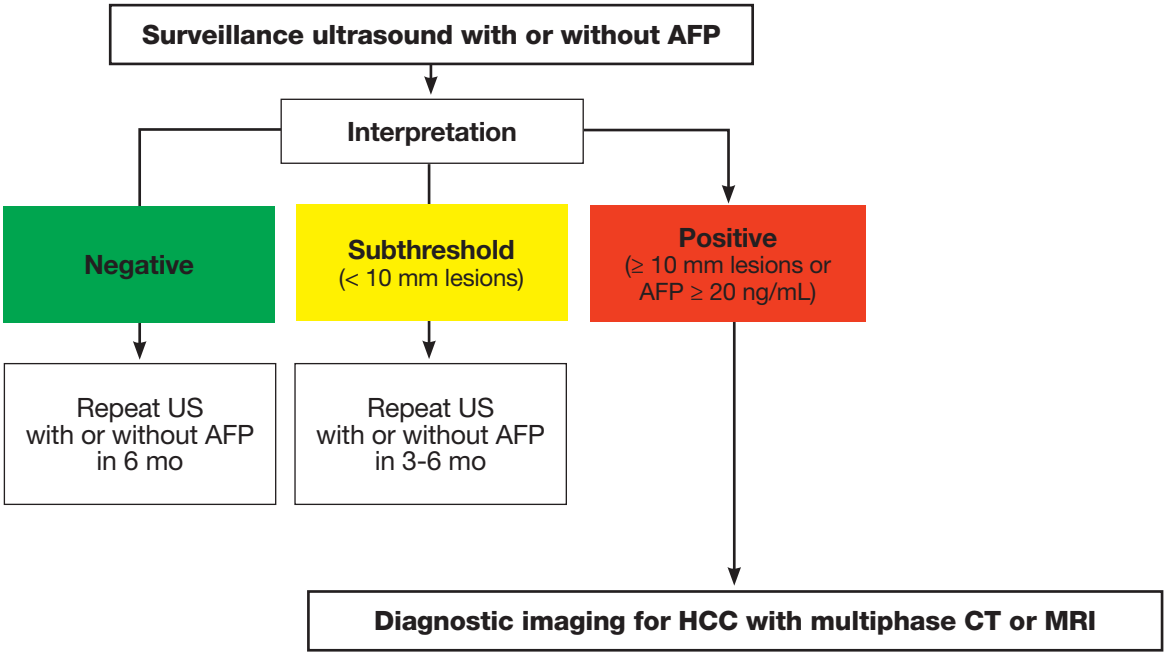
TABLE 2. **AASLD Surveillance Guidelines: Incidence of HCC Based on Individualized Risk Factors**[14]

Population Group	Threshold for Efficacy of Surveillance (< 0.25 LYG, % per year)	Incidence of HCC, %
Known Benefit		
Asian male HBV carriers > age 40	0.2	0.4 to 0.6 per year
Asian female HBV carriers > age 50	0.2	0.3 to 0.6 per year
HBV carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American Black people with HBV	0.2	HCC occurs at a younger age
HBV carriers with cirrhosis	0.2 to 1.5	3 to 8 per year
HCV cirrhosis	1.5	3 to 5 per year
Stage 4 PBC	1.5	3 to 5 per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably > 1.5 per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably > 1.5 per year
Other cirrhosis	1.5	Unknown
Surveillance Benefits Uncertain		
HBV carriers < age 40 (male patients) or < age 50 (female patients)	0.2	< 0.2 per year
HCV and stage 3 fibrosis	1.5	< 1.5 per year
• NAFLD without cirrhosis	1.5	< 1.5 per year

Legend: AASLD, American Association of Liver Disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LYG, life-years gained; PBC, primary biliary cholangitis.

Source: Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2018;68:723-750.

FIGURE 2. **AASLD Guidelines for HCC Surveillance**[14]



Legend: AASLD, American Association of Liver Disease; AFP, alpha fetoprotein; mo, months; US, ultrasound.

Source: Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2018;68:723-750.

opportunity to identify patients at increased risk and screen them regularly for liver lesions.[1,14] This allows early detection when the disease may be less invasive, increasing available treatment options and improving overall survival rates.[17]

Guidelines from professional societies, including the American Association for the Study of Liver Diseases (AASLD) and the National Comprehensive Cancer Network (NCCN), recommend HCC surveillance for at-risk patients.[14,15] **TABLE 2** outlines the AASLD guidelines regarding who should be enrolled in HCC surveillance programs based on their risk, potential benefit, and cost-effectiveness. Recommendations include surveillance for HBV carriers of several racial groups, including Asian, African, or North American Black. Patients with HBV or HCV and cirrhosis should also be screened, as well as patients with other conditions associated with cirrhosis (eg, NAFLD, NASH, hemochromatosis, alpha-1 antitrypsin deficiency, primary biliary cholangitis). Although NAFLD or NASH without cirrhosis are also associated with an increased risk for HCC, the precise benefit of surveillance for these patients remains unclear.[14]

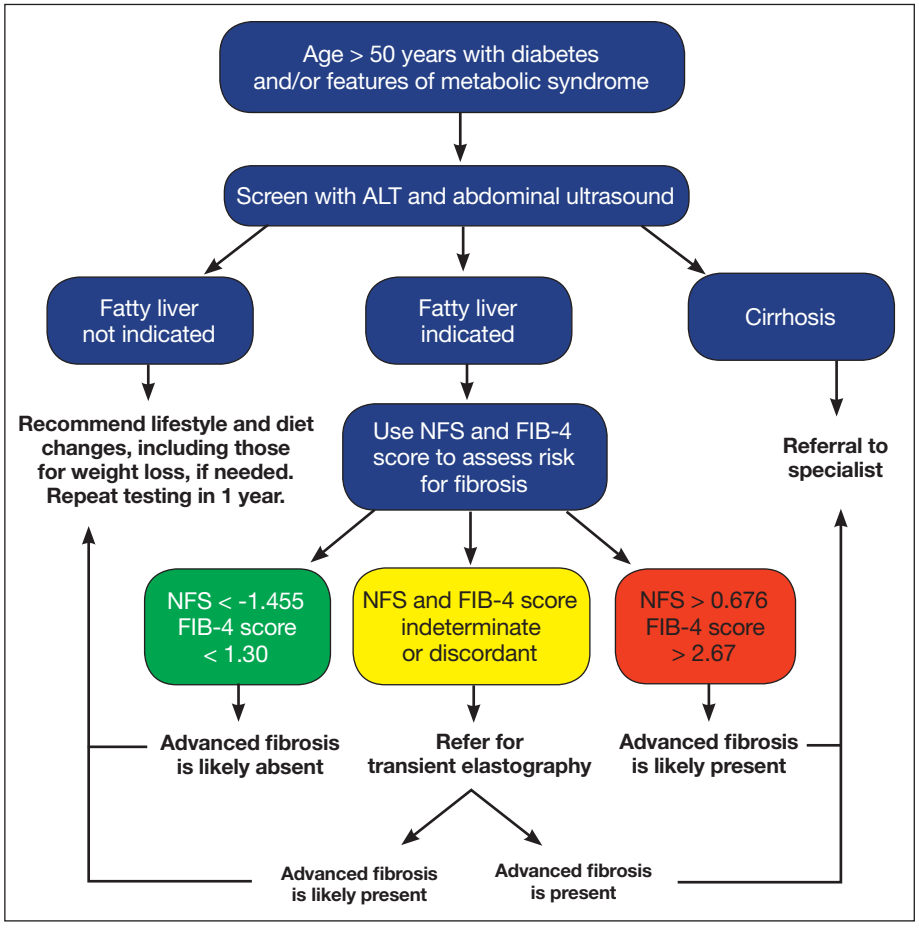
For candidates of HCC surveillance, AASLD guidelines recommend ultrasound imaging of the abdomen, with or without assessment of alpha fetoprotein (AFP), every 6 months. Interpretation of screening results is outlined in **FIGURE 2**. If the ultrasound shows new liver nodules < 10 mm in size, the recommendation is to repeat the ultrasound with or without AFP testing in 3 to 6 months. If a lesion ≥ 10 mm is found or the AFP level is ≥ 20 ng/ml, diagnostic imaging is recommended using multiphasic, cross-sectional computed tomography (CT) or magnetic resonance imaging (MRI). Surveillance should only be performed in patients who would be eligible and potentially benefit from treatment if a liver lesion was found.[14]

Current NCCN screening guidelines recommend the same timing and interpretation of results for patients at risk for HCC. In contrast to the AASLD guidelines, the NCCN also recommends HCC screening for patients with HBV in the absence of cirrhosis based on sex and age (female patients over age 50 and male patients over age 40).[15]

THE GASTROENTEROLOGIST'S AND PCP'S APPROACH TO HCC SURVEILLANCE

Optimal management of individuals at risk for liver cancer often involves care from a multidisciplinary team that includes primary care physicians, hepatologists, gastroenterologists, oncologists, surgical oncologists, transplant surgeons, radiation oncologists, diagnostic radiologists,

FIGURE 3. **Screening for NAFLD**[18]



Legend: ALT, alanine aminotransferase; FIB-4, Fibrosis-4; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score.

Source: Reproduced from Pandyarajan V, Gish RG, Alkhouri N, Noureddin M. screening for nonalcoholic fatty liver disease in the primary care clinic. *Gastroenterol Hepatol (N Y)*. 2019;15:357-365.

pathologists, nurses, and palliative care professionals.[14] Patients should be referred to specialists when needed and good lines of communication between clinicians should be maintained. Primary care physicians, gastroenterologists, and hepatologists should discuss a patient's individualized risk for HCC, taking into account such factors as obesity, diabetes, alcohol use, and geographically-related risk for viral infections. This allows determination of an appropriate screening approach, which should always follow current guidelines.[14,15]

Primary care physicians and gastroenterologists play a vital role in the identification of patients who should undergo surveillance. The early signs of liver disease and cirrhosis may be subtle, including fatigue, pain, and loss of appetite, so patients should be proactively assessed and monitored. Primary care physicians and gastroenterologists do not need to wait for a patient to experience signs and symptoms of HCC to refer patients for diagnostic imaging. If patients have underlying liver disease, gastroenterologists and hepatologists should develop a management plan that includes appropriate HCC surveillance.

Gastroenterologists also play an important role in the identification and management of patients with NAFLD (**FIGURE 3**). Fatty liver disease is often asymptomatic initially, suggesting screening for NAFLD is an important first step in finding patients who might be at risk for liver cancer. Patients over age 50 with diabetes or features of metabolic syndromes like hyperlipidemia, hypertension, or obesity should be screened for NAFLD using alanine aminotransferase (ALT) levels and abdominal ultrasound.[18] If the abdominal ultrasound shows evidence of liver cirrhosis, patients should be immediately referred to a specialist.[18]

If the abdominal ultrasound shows a fatty liver, patients should be evaluated using the NAFLD Fibrosis Score and Fibrosis-4 (FIB-4) testing to determine their risk for liver fibrosis (**FIGURE 3**). If these tests suggest fibrosis, patients should be referred to a specialist. If these tests are indeterminate or discordant, a FibroScan test or transient elastography can be used to assess fibrosis and determine the optimal next steps. A gastroenterologist or hepatologist can confirm the extent of fibrosis and determine if there are other underlying causes of liver fibrosis. Once NAFLD has been confirmed, patients are often referred back to their primary care physician for continued monitoring and HCC surveillance.[18]

There are several important challenges and potential barriers to HCC surveillance, most often related to the burden of screening. Patients need to be screened every 6 months and abdominal ultrasound typically takes several hours to complete. This requires patients to take time off work and travel to the clinic, which can feel unnecessary to asymptomatic patients who are feeling well. Clinicians should provide patients with effective education on the

importance and benefit of screening and set up reminders to improve patient compliance. Ongoing investigation of better biomarkers and blood-based screening approaches continues, as AFP testing alone is currently not recommended for surveillance.[14]

Ultimately, PCPs and gastroenterologists need to recognize that asymptomatic patients may have underlying liver disease that could lead to HCC. Patients need to be screened for HBV and HCV, as well as NAFLD. Patients with liver disease should be managed appropriately, incorporating HCC surveillance every 6 months.[14]

THE ONCOLOGIST'S APPROACH TO HCC SURVEILLANCE

As mentioned previously, HCC is an opportune disease for screening and early intervention, as the risk factors are relatively well-defined. All patients should be carefully observed for signs of cirrhosis or underlying liver disease, as we can only find liver cancer if we first find liver disease. Clinicians need to have a high suspicion for patients who have abnormal liver function tests or a personal history that puts them at risk for one of the known etiologies of HCC.[1]

With regards to risk for HBV and HCV infection, clinicians need to consider where patients were born and where their families are from, as HBV is typically transmitted mother to child and is more common in certain regions of the world.[1] HCV infection is typically acquired later in life through blood transfusions or intravenous drug use and current recommendations indicate patients should be screened for HCV at least once in their lifetime.[19] Patients with asymptomatic thrombocytopenia should be evaluated for potential underlying liver disease.[20] Those with obesity and/or diabetes mellitus should also be carefully monitored, following up on any abnormal laboratory tests such as liver enzyme elevations or thrombocytopenia.

Early diagnosis of HCC through active surveillance programs can greatly improve patient outcomes, including survival.[17] Liver lesions detected early are more likely to be amenable to surgical resection or patients may be eligible for liver transplantation. Beyond resection, radiofrequency ablation, microwave ablation, and cryoablation are potential curative approaches for patients with early-stage disease.[15] Although HCC is common and associated with a very poor prognosis, proactive surveillance can help ensure that patients are identified early and receive optimal care.

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