HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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Insights on the Risk of Hepatocellular Carcinoma in Patients With Nonalcoholic Steatohepatitis

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G&H What is the prevalence of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis?

AS Hepatocellular carcinoma (HCC) is the 7th most common cancer worldwide, with approximately 500,000 new cases per year. Historically, the most common causes of HCC have been hepatitis B (in East Asia and Africa) and hepatitis C (in Europe and the United States). However, the prevalence of nonalcoholic steatohepatitis (NASH)-related HCC has steadily increased over time, paralleling increases in metabolic syndrome, and now accounts for 10% to 20% of HCC cases in many centers. Modeling studies have suggested that the prevalence of NASH-related HCC will continue to rise over the next decade, increasing by more than 100% in the United States. Furthermore, metabolic syndrome components, such as diabetes and obesity, increase HCC risk in patients with other liver disease etiologies, so the total population attributable fraction of metabolic syndrome to HCC burden in the United States has been estimated to exceed 30%.

G&H What is the role of cirrhosis in terms of HCC risk in patients with NASH?

AS Across all etiologies, one of the strongest risk factors for HCC is the presence of cirrhosis, and the same is true for patients with NASH. Although 25% to 30% of NASH-related HCC occurs in the absence of cirrhosis, the incidence of HCC among patients with noncirrhotic NASH is very low, below 0.1% per year. In contrast, HCC risk in patients with NASH cirrhosis is substantially higher, at approximately 1% to 2% per year. However, there is wide heterogeneity in risk within both of these categories (presence vs absence of cirrhosis), highlighting the need for more nuanced risk stratification tools in the future.

G&H How strong are nonmodifiable risk factors such as age, sex, and genetics in terms of HCC risk in the setting of NASH?

AS Older age and male sex are 2 of the strongest risk factors for HCC across all liver disease etiologies, including NASH. Sex disparities in HCC incidence are likely related to differences in the prevalence of risk factors (eg, viral hepatitis, metabolic syndrome, alcohol abuse) as well as differences in sex hormones. Several genetic single nucleotide polymorphisms, such as *PNPLA3* and *MBOAT7*, have been associated with HCC risk, particularly among patients with NASH. However, it is unclear how much genetic risk scores would add to clinical risk models incorporating readily available risk factors, such as age, sex, race and ethnicity, metabolic syndrome features, and degree of liver dysfunction.

G&H How strong are modifiable risk factors such as alcohol, diet, and smoking in terms of HCC risk in this patient population?

AS In terms of modifiable risk factors, the most important to consider are active viral hepatitis, ongoing alcohol use, and metabolic syndrome. It is very important to recognize and treat these risk factors to reduce the risk of HCC. Several large studies have consistently demonstrated that treatment of hepatitis B or C infection significantly reduces HCC risk by more than 75%. Similarly, it is recommended that patients stop drinking alcohol and control metabolic syndrome features, including diabetes.

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Although smoking is a modest risk factor for HCC, its population attributable fraction is likely fairly large given how common smoking remains in many populations. Unfortunately, high-quality studies evaluating diet and cancer risk are very difficult to conduct, so clinicians are forced to depend on epidemiologic studies identifying potential associations. These studies have suggested that adherence to the Mediterranean diet and high intake of vegetables, fish, monounsaturated fats, and micronutrients are associated with lower HCC risk. In addition, there have been several studies showing decreased risk of HCC with coffee.

Thus, among all of the aforementioned risk factors for HCC, the presence of cirrhosis from any etiology is the strongest and then the other traditional factors of older age, male sex, metabolic syndrome components, and health behaviors such as alcohol use and smoking.

G&H Why is it important to assess the risk of HCC in patients with NASH?

AS Assessing HCC risk is important not only in terms of prognostication when talking with patients but also in terms of direct implications for HCC surveillance. Recent modeling data suggest that HCC surveillance is cost-effective when HCC risk exceeds 1% in the setting of cirrhosis and 0.2% in the absence of cirrhosis. HCC risk exceeds this threshold in patients with NASH cirrhosis but not in those without cirrhosis. HCC surveillance in high-risk patients is critical, as it has been associated with significantly increased early tumor detection, receipt of curative treatment, and improved survival.

G&H How can an individual patient's risk for HCC be best assessed?

AS All patients with NASH should undergo evaluation to assess their stage of fibrosis, which can be done using one of several available noninvasive tests, including blood-based measures (eg, the Fibrosis-4 index or FibroTest), transient elastography, or magnetic resonance elastography. By assessing the stage of fibrosis, clinicians can identify patients who have cirrhosis, who thereby warrant HCC surveillance.

G&H What research has been conducted thus far using biomarkers or scores to determine HCC risk?

AS Several studies have derived and tested clinical risk scores, and there has been some early research evaluating serum biomarkers for HCC risk stratification in patients with cirrhosis, including those with NASH. For example, Ioannou and colleagues have examined a clinical risk model that included 7 factors (age, sex, diabetes, body mass index, platelet count, serum aspartate aminotransferase, and alanine aminotransferase), and Fujiwara and colleagues have examined the serum biomarker score PLSec-AFP for HCC risk. However, the concordance statistics for the models were approximately 0.75, and both models still require external validation in large cohorts of patients with NASH cirrhosis. Although there are promising candidates in the pipeline, none of the scores or biomarkers have been sufficiently validated for routine use in clinical practice yet.

G&H Should any patients who have noncirrhotic NASH undergo HCC surveillance at this time?

AS As discussed, the annual incidence of HCC in patients with noncirrhotic NASH is low, so HCC surveillance is not cost-effective in this group of patients. At this time, surveillance is restricted to patients with cirrhosis, who have an annual risk of HCC between 1% to 2% per year. If risk stratification tools can be sufficiently validated in the future, the hope is that clinicians will be able to identify a high-risk subgroup of patients with noncirrhotic

NASH who have sufficiently high risk to warrant HCC surveillance.

G&H Which surveillance modalities are best, particularly in patients with NASH who are obese?

AS Current guideline recommendations from the American Association for the Study of Liver Diseases are to perform abdominal ultrasound with the serum biomarker alpha-fetoprotein every 6 months. However, ultrasound is operator-dependent and can have poor visualization, resulting in lower sensitivity, in approximately 20% of patients, particularly obese individuals and those with NASH-related cirrhosis. This has raised the question of which alternative surveillance modalities can be used in these patients. Although there has been a lot of research on emerging biomarkers as well as magnetic resonance imaging (MRI)-based surveillance strategies, unfortunately, none have been sufficiently validated for routine use at this time. Thus, guidelines recommend starting with ultrasound-based surveillance, and if there is poor visualization or other notable limitations, MRI-based surveillance can be considered.

G&H Has it been shown that lifestyle modifications such as weight loss and increased physical activity can reduce the risk of HCC in patients with NASH?

AS Studies have demonstrated an association between healthy behaviors, including lower weight and higher physical activity, and decreased HCC risk. Weight loss is a cornerstone for NASH therapy and has been shown to improve liver-related outcomes, but there are fewer data demonstrating that it specifically reduces HCC risk. However, the lack of data specifically for HCC risk does not diminish the importance of these healthy behaviors for patients with NASH.

> Early identification of patients with NASH, prior to the development of cirrhosis, is the best way to reduce liver-related mortality and prevent HCC.

G&H Is there any evidence that chemopreventive treatments such as aspirin, antidiabetic treatments, and statins can reduce the risk of HCC?

AS Large cohort studies have suggested that aspirin, statins, and metformin, as well as coffee, have an association with decreased HCC risk. However, those studies have potential issues with residual confounding, and it is unclear whether they show a causal relationship. Thus, at this time, the strength of evidence is not sufficient to recommend aspirin, statins, or metformin solely for chemoprevention. Of course, these medications should be used if they are otherwise indicated, which is the case for many patients with NASH. The only therapy that is currently included in the European Association for the Study of the Liver guidelines for HCC chemoprevention is coffee, which has a similar level of evidence as the aforementioned medications, but has a more favorable risk-benefit ratio.

G&H Can clinicians use any other strategies to help reduce the risk of HCC in patients with NASH?

AS Early identification of patients with NASH, prior to the development of cirrhosis, is the best way to reduce liver-related mortality and prevent HCC. This allows clinicians to intervene with lifestyle modifications, as well as other treatments as they become available, to prevent patients from developing cirrhosis, thereby reducing the risk of HCC.

There is sometimes a misconception that mildly elevated liver function tests are benign and do not have untoward consequences. However, this can often be the first sign that a person has chronic liver disease, often NASH. When a patient first presents with evidence of NASH, it is important to intervene at that stage; even though there is a dearth of effective pharmacologic treatments, lifestyle modifications can still be efficacious to improve prognosis in these patients.

G&H How can NASH patients who develop HCC be managed best?

AS HCC has the best prognosis when found early. At that stage, there are curative therapies, including surgical resection, liver transplantation, or local ablation. Thus, it is very important for all at-risk patients to undergo surveillance to maximize the likelihood of early tumor detection. Unfortunately, HCC surveillance is often underused among patients with cirrhosis, with the lowest surveillance utilization in patients with NASH. All

patients who develop HCC are best treated in a multidisciplinary manner, with surgeons, hepatologists, interventional radiologists, and medical oncologists who can appropriately stage the patient and help deliver curative treatments whenever possible.

G&H What are the next steps in research in terms of HCC risk and NASH?

AS Risk stratification tools would allow clinicians to identify patients who have the highest risk for HCC, who should undergo more-intensive surveillance strategies. These tools may be particularly helpful in patients with noncirrhotic NASH to identify the subgroup with higher HCC risk that would benefit from surveillance. The tools may also facilitate identification of patients with low HCC risk, who may not warrant surveillance. Accurate risk stratification tools would therefore help lead to a precision surveillance strategy for NASH patients instead of the current one-size-fits-all approach. Risk stratification tools may also identify a subgroup of patients who would also benefit from chemoprevention and who could serve as potential subjects for future chemoprevention trials.

Disclosures

Dr Singal has served as a consultant or on advisory boards for Bayer, Wako Diagnostics, Exact Sciences, Roche, Glycotest, and GRAIL.

Suggested Reading

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