

# HCC IN FOCUS

Current Developments in the Management of Hepatocellular Carcinoma

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## Risk of Hepatocellular Carcinoma in Patients With Nonalcoholic Steatohepatitis



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**G&H** How common are nonalcoholic steatohepatitis and hepatocellular carcinoma in the United States, and how often do they coexist in a patient?

**MC** Fatty liver disease as a whole is estimated to affect approximately 80 to 90 million Americans. However, nonalcoholic steatohepatitis (NASH) likely affects only approximately 30% of that number. Approximately 5% of patients with NASH progress to cirrhosis at some point. Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer deaths in the United States and is increasing at a substantial rate. Approximately half of HCC cases occur in patients who have a profile suggestive of fatty liver disease.

**G&H** Has there been a recent increase in the number of patients with both diseases?

**MC** Unquestionably. The number of patients with fatty liver disease, including those with NASH, has risen in parallel with an increase in the prevalence of obesity, not just in the United States but worldwide. The frequency of HCC has also increased in recent years. It is widely thought that the increases in fatty liver disease and obesity have contributed to the increase in HCC.

**G&H** What is the current understanding of the relationship between NASH and HCC?

**MC** Any chronic liver disease that can progress to cirrhosis is associated with an increased risk of HCC,

whether it is viral hepatitis, NASH, or a metabolic liver disease other than NASH, for example. When these diseases progress to cirrhosis, the frequency of liver cell turnover and genetic abnormalities that accompany frequent mitosis over time are thought to put patients at risk for HCC. In addition, fatty liver disease is generally associated with obesity and hyperinsulinemia. In part through farnesylation of Ras proteins, high levels of insulin, which is a mitogenic hormone, may contribute to the increased risk of HCC in patients with fatty liver disease. A very small number of patients with HCC and fatty liver disease do not require progression to cirrhosis to develop HCC.

**G&H** What are the specific mechanisms that might trigger HCC in patients with NASH?

**MC** Several potential mechanisms can contribute to the increased risk of developing HCC in patients with NASH. In addition to chronic hyperinsulinemia, these mechanisms include dysbiosis of gut microbiota, changes in bile acids, and the presence of genes associated with histologically progressive NASH. The gut microbiota may promote HCC through toll-like receptor 4 activation. Circulating levels of deoxycholic acid, an oncogenic bile acid, are elevated in patients with NASH. Polymorphisms in 2 genes that are more prevalent in patients with NASH, patatin-like phospholipase domain-containing 3 (*PNPLA3*) and transmembrane 6 superfamily member 2 (*TM6SF2*), have been associated with an increased risk of HCC through unclear mechanisms.

### G&H What are the most common risk factors for HCC in the setting of NASH?

**MC** Without question, the most common risk factors are the development of cirrhosis and then age and comorbidities, such as cardiovascular disease and concomitant alcoholic liver disease or viral hepatitis.

### G&H What is the role of biomarkers in determining the risk of HCC in these patients?

**MC** Currently, the American Association for the Study of Liver Diseases recommends initial screening (via ultrasound and  $\alpha$ -fetoprotein levels) of patients with cirrhosis from any cause. These tests should be repeated for further HCC surveillance every 6 months.

In addition, promising emerging data have suggested that the sensitivity and specificity of HCC screening could be increased by calculating the GALAD score (gender, age, Lens culinaris agglutinin-reactive  $\alpha$ -fetoprotein,  $\alpha$ -fetoprotein, and des- $\gamma$ -carboxyprothrombin). The GALAD score can be used to determine the percentage likelihood that an individual patient with cirrhosis has HCC at a particular time. The results may affect the type and frequency of imaging performed. For example, a patient in whom the GALAD score corresponds to an HCC risk of at least 20% might undergo a liver protocol rather than, or in addition to, a less-sensitive and -specific ultrasound.

### G&H Is there consensus on how often NASH patients should undergo screening for HCC?

**MC** Current guidelines for HCC screening from the major medical societies are fairly consistent on this issue, recommending both ultrasound examination of the liver and  $\alpha$ -fetoprotein measurement every 6 months.

### G&H Should NASH patients without cirrhosis undergo HCC screening as well?

**MC** No. This issue was considered by several medical societies, including the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver, and there is consensus that patients with fatty liver disease who do not have cirrhosis should not undergo routine screening for HCC. The frequency of HCC in these patients is too low to justify screening at this time.

### G&H What is the best imaging modality for screening these patients?

**MC** The most cost-effective imaging method is standard ultrasound. The most sensitive method is triphasic computed tomography (CT) scanning or magnetic resonance (MR) imaging with liver protocol. Agents such as gadolinium can add to the sensitivity of MR imaging. Thus, a patient who has abnormal ultrasound findings or has normal ultrasound findings but a high level of suspicion of HCC based on biomarkers should undergo follow-up CT or MR imaging. Surveillance for HCC after a negative screening should be performed every 6 months with ultrasound.

### G&H Are there any methods to prevent or reduce the development of HCC in NASH patients?

**MC** There are no prospective data showing an effective intervention to reduce the likelihood or risk of HCC in NASH patients. Having said that, in other diseases frequently associated with HCC and cirrhosis (eg, hepatitis B or C virus infection), successful treatment of the underlying liver disease using antiviral therapies greatly reduces the risk of HCC. Thus, our hope is that through dietary intervention and weight loss, or success of one of the pharmacologic agents currently in development, patients may be able to reduce the presence of the nonalcoholic state of hepatitis, which might also decrease the risk of HCC over time. However, this is currently entirely hypothetical.

### G&H Are there any special considerations that should be kept in mind when managing NASH patients at risk for developing HCC?

**MC** Patients with NASH frequently have a body habitus that might reduce the sensitivity and specificity of ultrasound. Using ultrasound for imaging of the liver is challenging if a patient has a lot of abdominal adipose. Fat within the liver can also decrease the granularity or accuracy of the images that are generated through ultrasound. Thus, the possibility of performing a CT scan or MR imaging with liver protocols should be considered in patients in whom imaging is seen to be suboptimal with ultrasound or if there is an above-average level of suspicion for HCC.

### G&H If NASH patients do develop HCC, how should they be managed? Should management differ from that of HCC patients without NASH?

**MC** Currently, HCC management should be exactly the same in both groups. There are excellent protocols for HCC management, including by the American

Association for the Study of Liver Diseases and the European Association for the Study of the Liver, that should be applied to HCC patients with and without NASH. For example, if a patient has liver disease that is compensated and has no significant portal hypertension, liver resection should be performed when not otherwise contraindicated. Patients who have T2 stage disease or who are within the Milan criteria (or only slightly beyond) should be considered for liver transplantation with locoregional bridging therapy. Patients who are not eligible for liver transplantation can attempt to undergo downstaging of the tumor burden to make liver transplantation a consideration. For patients in whom downstaging is not successful, there are new therapies that involve checkpoint inhibition, approved therapies with mixed kinase inhibitors such as sorafenib (Nexavar, Bayer), and several other emerging molecular therapies.

It should be noted that it is often mistakenly thought that patients with a high body mass index or medically complicated obesity are not candidates for surgery, including liver transplantation. However, the idea that a high body mass index or greatly excessive weight is an unchangeable contraindication to liver transplantation is not supported by the literature. There are a number of approaches, including weight loss surgery at the time of liver transplantation and intensive approaches to lifestyle modification and weight loss before liver transplantation, that can change the ability of a patient to go through with surgery.

### G&H What are the next steps in research?

**MC** One of the most important next steps is to identify screening strategies for patients with cirrhosis and

NASH that are optimally effective. As with cirrhosis due to hepatitis B infection, it is possible that the HCC screening strategy needs to be tailored to individual patient profiles. In addition, I do not know whether the current ultrasound algorithms will be as effective in patients with the body habitus often associated with NASH, compared to non-NASH populations. It is also important to further explore the utility of biomarkers, including the new GALAD score, and the optimization of the relatively recently approved therapies, including checkpoint inhibitors, sorafenib, and regorafenib (Stivarga, Bayer). These agents have been approved for use individually, but researchers should explore how the drugs would work in combination and what would constitute ideal combinations, including possible associations with locoregional therapies such as radioembolization and chemoembolization.

*Dr Charlton has no relevant conflicts of interest to disclose.*

### Suggested Reading

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