Who Remains at Risk for Liver Cancer After Hepatitis C Is Cured?

People who achieved SVR two or more years ago were less likely to develop hepatocellular carcinoma than those cured more recently.

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People who are cured of hepatitis C have a much lower likelihood of developing liver cancer, but their risk does not fall to zero. The incidence of liver cancer declines over time after successful treatment, but some people remain at risk and can benefit from screening, researchers reported at the American Association for the Study of Liver Diseases (AASLD) Liver Meeting.

Over years or decades, hepatitis C virus (HCV) can lead to serious complications, including liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC), the most common type of liver cancer. HCC is often detected at a late stage and is difficult to treat, making it a leading cause of cancer-related death worldwide. AASLD guidelines recommend that people with cirrhosis should undergo regular surveillance to detect liver cancer at an early stage, but screening for patients without cirrhosis remains controversial.

Liver Cancer After a Cure

Naveed Janjua, MBBS, DrPH, of the British Columbia Centre for Disease Control, and colleagues explored the impact of sustained virological response (SVR) to direct-acting antiviral (DAA) treatment on HCC risk among people with and without cirrhosis. SVR, or continued undetectable HCV viral load after completion of treatment, is considered a cure.

The researchers analyzed data from the British Columbia Hepatitis Testers Cohort, which includes approximately 1.5 million people tested for HCV or HIV, and cases of hepatitis B or C, HIV or tuberculosis reported to the public health system since 1990.

A total of 10,118 people treated with DAA therapy were matched with an equal number of people with hepatitis C who did not receive treatment. Of those treated, 97% achieved SVR. The participants were followed for a median of about 1.8 years.

The HCC incidence rate was 5.7 cases per 1,000 person-years among people who achieved SVR, compared with 58.6 cases among people who were treated but not cured and 12.7 cases among untreated people. In all three groups, liver cancer incidence was higher for people who had progressed to cirrhosis (20.5, 187.2 and 53.5 cases per 1,000 person-years, respectively).

In a multivariate analysis, SVR was associated with a substantial reduction in HCC risk compared with the untreated group, and this effect was stronger among people who did not have cirrhosis at the time of treatment. Older age was also associated with a higher risk for liver cancer following SVR.

“These results highlight the continued need for early treatment [to] realize the fuller benefits of DAA treatment to prevent development of advanced stage liver disease,” the researchers concluded.

HCC Risk Falls Over Time

Most studies to date have looked at the development of liver cancer over a fairly short time period after hepatitis C treatment. Philip Vuiten, MD, of the University of Washington Medical Center in Seattle, and colleagues asked whether HCC risk declines over time after achieving SVR. If this is the case, people who are successfully treated may eventually have a low enough risk that the costs and harms of screening exceed the benefits, Vuiten suggested.

This analysis included 75,965 people with hepatitis C managed by the Veterans Affairs health care system who had achieved SVR and were still alive, had not undergone liver transplantation and had not developed HCC prior to January 2018. They were followed through the end of 2019. Almost all were men, and the average age was approximately 65 years. Just over a quarter had cirrhosis. People who were cured more than six years ago were more likely to have HCV genotypes 2 or 3, which are easier to treat.

Overall, 547 participants developed liver cancer during follow-up, but the risk was higher for people with cirrhosis. Among those with cirrhosis, HCC incidence was highest for those who achieved SVR one or two years ago (2.71 cases per 100 person-years), lower for those who were cured two to four years ago (2.11 cases) and lowest for those who were cured four to six years ago (1.65 cases) or more than six years ago (1.68 cases).

After adjusting for other factors, people with cirrhosis who were cured two to four years ago were 21% less likely to develop HCC, and those who were cured more than four years ago were 38% less likely, compared with those who were cured one or two years ago. But among people without cirrhosis, there was no significant association between HCC risk and time since SVR.

For people with cirrhosis, HCC risk decreases as time after SVR increases, but this effect appears to bottom out at about six years. Nonetheless, the risk remains “substantial,” at approximately 1.7% per year. Using a cost-effectiveness cutoff of about 1.5%, HCC risk remains high enough even six years after being cured to warrant ongoing screening, the researchers concluded.

People Without Cirrhosis

While cirrhosis is clearly a major risk factor for liver cancer, some people without advanced fibrosis can still develop HCC after successful hepatitis C treatment. Cirrhosis is the most severe stage of fibrosis, or liver scarring.

Yuki Tahata, MD, of Osaka University Graduate School of Medicine, and colleagues aimed to develop a scoring system to predict the likelihood of liver cancer in people without advanced fibrosis, which could help clinicians identify those who need HCC screening.

This analysis included 1,682 people with hepatitis C at 26 Japanese hospitals who did not have advanced liver fibrosis. They started DAA treatment between September 2014 and October 2020 and achieved SVR. People with hepatitis B or HIV, those with a history of liver cancer prior to SVR and liver transplant recipients were excluded. About 60% were women, and the median age was 66 years.

The participants underwent HCC surveillance using abdominal ultrasound prior to DAA treatment, at the end of treatment and every six months thereafter. A total of 28 people developed liver cancer during follow-up. The cumulative HCC incidence rates at one, three and five years after SVR were 0.6%, 1.8% and 2.5%, respectively.

In a multivariate analysis, the factors that were significantly associated with HCC incidence after being cured were older age (65 or over), elevated ALT liver enzymes and elevated alpha-fetoprotein levels at the time of SVR.

This enabled the researchers to develop a scoring system to predict the likelihood of liver cancer after SVR, allocating one point for each of these factors. The cumulative HCC incidence rates at one, three and five years post-SVR were 2.9%, 6.0% and 7.9%, respectively, for people with a score of 2 or 3. For those with a score of 1, the corresponding rates were 0.5%, 2.1% and 2.9%. But no patients with a score of 0 developed HCC.

“We developed a new scoring system using these three factors to enclose patients who need HCC surveillance after SVR, and this score may be useful for stratification of HCC risk in patients without advanced liver fibrosis,” the researchers concluded.

Click here to read Vuiten’s abstract.
Click here to read Tahata’s abstract.

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