

Tamar Taddei, MD

# Adapting to the Changing Liver Cancer Landscape

**In the United States, hepatitis C** has long been the number one driver of hepatocellular carcinoma (HCC), the most common liver cancer and the fourth-leading cause of cancer-related deaths worldwide. Between three to five million Americans are living with chronic hepatitis C, but 4 in 10 do not realize they have it. More than 75 percent of patients are baby boomers, whose many years of undetected liver damage from hepatitis C make them particularly vulnerable to HCC.

In recent years, the liver cancer landscape has been rapidly changing in the United States. Skyrocketing hepatitis C cases, the emergence of a worrying new at-risk group for hepatitis C, and a surge in non-viral etiologies of HCC are presenting Yale Cancer Center researchers and clinicians with new challenges and opportunities in their approach to patient outreach and treatment.

In April 2020 the CDC announced that new hepatitis C cases in the U.S. are four times higher than they were a decade ago. In addition, adults 20 to 39 years old now have the highest rates of new cases. In response, the CDC changed its testing recommendations, advising all adults to be tested for hepatitis C at least once.

“The opioid epidemic is causing this very high prevalence among millennials,” explained Tamar Taddei, MD, Associate Professor of Medicine (Digestive Diseases) and Director of the Liver Cancer Program at VA Connecticut Healthcare System. Hepatitis C is usually spread through blood, often from injection drug use. Opioid users commonly progress from prescription oral medications to injection drugs. “These younger people need to get tested and treated for hepatitis C immediately,” Dr. Taddei said. “There’s now a very effective

cure for hepatitis C; we don’t want them to develop cirrhosis or liver cancer.”

Since 2014, direct-acting antivirals (DAAs) have become the standard of care for hepatitis C. “You can’t underestimate the historical importance of the rise of oral DAA therapy and its impact on clinical management and overall epidemiology of hepatitis C,” said Joseph Lim, MD, Director of the Yale Viral Hepatitis Program. “We’re able to cure over 90 percent of patients with hepatitis C with these two- to three-month oral regimens and substantially reduce the risk of liver cancer and need for liver transplantation.”

However, patients who already have cirrhosis are still at risk for liver cancer even after they are cured of hepatitis C. Using national VA electronic medical record data, Dr. Taddei and colleagues analyzed records of more than 48,000 VA patients who were cured of hepatitis C with antiviral treatment. Patients with stage 3 or 4 liver fibrosis at the time of treatment continued to have a high -risk of HCC for up to 10 years. The duration was startling. “These patients should still receive liver cancer screening with an ultrasound every six months. It’s vital they continue, because if HCC is diagnosed at an early stage it is curable,” she explained.

In a separate study, Dr. Taddei found that patients with cirrhosis benefitted from the use of statins, drugs which reduce lipids in the blood but may also have a favorable effect on portal hypertension. “Portal hypertension, or high blood pressure in the liver – the consequence of cirrhosis – leads to severe complications,” she said. “People in our observational study on statins lived longer. We next want to see whether

statins can prevent decompensation, when the scarring becomes so severe the liver starts to fail.” She has launched a four-year clinical trial in which half of the anticipated 500 patients enrolled will take simvastatin for two years, while the other half will take a placebo; both groups will be observed for two years for hepatic decompensation.

The elevated, sustained risk of HCC in patients with cirrhosis is often driven by diabetes and obesity. Those two risk factors are also behind an alarming increase in non-alcoholic fatty liver disease (NAFLD). “The sheer number of people at risk is impressive,” said Mario Strazzabosco, MD, PhD, Clinical Program Leader of Smilow Cancer Hospital’s Liver Cancer Program and Deputy Director of the Yale Liver Center. “Ten years ago, we thought NAFLD was a benign condition. But then we realized it can lead to cirrhosis, and in some cases, it can lead to liver cancer without cirrhosis. So it’s even more important to devise screening protocols that are both clinically effective and cost effective.”

In 2020, Drs. Lim and Strazzabosco contributed to screening and surveillance guidance for HCC in NAFLD patients. Their individual papers each recommended ultrasound to screen for HCC in NAFLD patients with cirrhosis.

“This is a story that is still being written, and there’s a lot of research that needs to be done,” said Dr. Strazzabosco. He is compiling a database of liver cancer patients to review their individual etiologies, treatments, and outcomes to improve clinicians’ decision-making for future patients. “You have to look at all the risk factors in a single patient in order to combat a successful fight against this cancer,” said Dr. Strazzabosco. “That is what we do in our program.”