

## FEATURE STORY

# Liver Cancer: More Cases, More Causes

BY JENNIFER M. GANGLOFF

John Emerson was an avid, healthy kayaker and outdoorsman when he learned he had hepatocellular carcinoma (HCC), or primary liver cancer, in May 2006. Six weeks after his diagnosis, Emerson was scheduled to have a resection to remove the diseased portion of his liver, but there wasn't enough healthy liver. Other therapies were attempted, including a clinical trial with a new targeted cancer drug, but his tumor continued to grow through the fall.

Emerson spent his last few months getting his financial affairs in order, saying goodbye to friends, soaking up as much from life as he could—and spending precious time with his new wife, Brenda, whom he married in August 2006.

“When I first found out that I had HCC, it stunned me,” Emerson told *CURE* prior to his death on February 8 at age 59. Emerson was among the small number of HCC patients whose histories don't fit into any of the major risk factor categories, which include the viruses hepatitis B and C and alcohol abuse.

Although researchers have made huge strides in cancer treatment in the past few decades, liver cancer remains largely untamed, resisting standard treatments. A recent highlight came in the form of a targeted agent called Nexavar® (sorafenib), which may soon become the first drug approved for advanced liver cancer after a phase III study found the drug extended survival.

Although doctors may have found a drug that lengthens patients' lives, HCC, sometimes called hepatoma, remains a highly aggressive cancer. HCC is a type of primary liver cancer that starts in the liver, in contrast to secondary, or metastatic, liver cancer that starts elsewhere in the body and spreads to the liver. Liver tumors, nourished with a rich supply of blood via the hepatic artery and their own blood vessels, can double in size in just three to six months and spread quickly to other organs.

While liver cancer is common on a global scale—close to 700,000 cases worldwide—it remains somewhat rare in the United States with about 18,000 Americans diagnosed in 2006. But the incidence has been rising over the past two decades and is expected to continue to increase for at least a couple more

decades. The growing incidence has led researchers to take a closer look at the origins of this deadly disease.

## Causes of HCC

The nature of the liver itself, at once both hardy and delicate, contributes to the difficulty of treating HCC. The two-lobed liver—about the size of a football—sits in the upper right quadrant of the abdomen, tucked under the ribs. The liver performs several vital functions, such as processing cholesterol, making bile (critical for digestion and fat absorption), helping the blood clot and detoxifying potentially poisonous chemicals, including alcohol and drugs.

Liver cancer experts attribute the rise in HCC to an increase decades ago in chronic infection with hepatitis C and hepatitis B, the most common risk factors along with chronic alcohol consumption. Infection with HCV peaked in the United States about 20 to 30 years ago, when blood transfusions weren't screened for disease and sharing of infected needles was common among drug users, says Ghassan Abou-Alfa, MD, a medical oncologist with the Gastrointestinal Oncology Service at Memorial Sloan-Kettering Cancer Center in New York.



John Emerson on Farmington River in Massachusetts in October 2006.  
Photo by Brenda Surabian Emerson

With about 170 million people worldwide infected with the more serious HCV, Americans make up close to four million, and another 1.4 million people in the United States and up to 400 million worldwide have HBV. But those infection rates are now declining, which may eventually drive down liver cancer rates. Dr. Abou-Alfa quickly cautions, however, that the decline may not be the end of the story.

Growing evidence suggests two other diseases now increasingly common in the United States may also be significant risk factors for primary liver cancer—obesity and diabetes. Precisely how they contribute to HCC is still under investigation, but both are known to cause nonalcoholic fatty liver disease, or liver cirrhosis, which Dr. Abou-Alfa and other experts believe will cause liver cancer incidence to continue to increase in years to come.

Liver cancer expert Hashem El-Serag, MD, associate professor of medicine at

Baylor College of Medicine in Houston, is studying possible genetic determinants of cancer related to obesity and insulin resistance. “The association between obesity and hepatocellular carcinoma is gaining intense interest due to the epidemic rates of obesity in the U.S. and several other Western countries,” he says.

While evidence indicates a higher risk of liver cancer among those who are obese, the possible interplay of diet, diabetes, fat distribution in the body and other factors must be clarified, he says. If the HCC association bears out, Dr. El-Serag warns “it may have serious implications.”

Other risk factors for primary liver cancer include hemochromatosis, a hereditary liver disease, and aflatoxins, a carcinogenic fungus found in improperly stored nuts and grains, which is screened for and banned in the United States but common in Southeast Asia and parts of Africa.

The common thread among these risk factors is cirrhosis, which can develop silently over decades. Cirrhosis, or permanent scarring of the liver, results from diseases that injure and kill normal liver cells repeatedly over a long period of time. But the pathway isn’t clear for the 5 percent of people with cirrhosis that leads to liver cancer.

Researchers believe chronic infection with HCV leads to liver injury, inflammation and increased cell turnover, which, in turn, can cause cellular transformations resulting in malignancies. In addition, the genetic material of the hepatitis B virus can insert itself into normal liver cells, causing mutations and excessive cell growth that can lead to cancer. Liver cancer cells often develop numerous genetic defects or mutations as they grow, which is one of the reasons liver cancer is so hard to treat—the target is constantly shifting, and what works for one person may not work for another.

HCC typically has no symptoms until later stages, which makes early diagnosis difficult, especially in people who don’t know they’re at risk, like John Emerson. When signs and symptoms do arise, they may include weight loss, fatigue, pain in the upper right abdomen that may extend to the back and shoulder, feeling full after small meals, accumulation of fluid in the abdomen (ascites), nausea, loss of appetite and jaundice.

### Treatment Challenge

No “standard” chemotherapy exists for HCC since studies have shown chemotherapy offers little, if any, survival benefit while posing a high risk of side effects. One reason for chemotherapy’s ineffectiveness is the cancer-causing cirrhosis, which impacts the liver’s ability to metabolize cancer drugs, rendering them ineffective.

The commonly used chemotherapy drug Adriamycin® (doxorubicin) may be more helpful than other medications with a response rate of 11 percent. But combining Adriamycin with cisplatin, interferon and 5-fluorouracil, a combination known as PIAF, has shown a response rate of up to 26 percent with an average survival of about nine months.

Experts say chemotherapy can be used to shrink tumors prior to surgical

resection, which can delay disease progression and make patients more comfortable by lessening pain and other symptoms. Although the liver can regenerate, resection (surgically removing the diseased portion of the liver) is an option for only about 10 to 15 percent of patients because cirrhosis affects the entire liver, decreasing its overall reserve capacity. At the same time, the liver is vulnerable to severe damage from chronic cirrhosis, and when operated upon, is prone to tearing and heavy bleeding.

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—Goran B. Klintmalm, MD, PhD

Patients without the option of surgical resection or liver transplant can look to other treatments that may extend life or relieve pain. These include ablation procedures that destroy tumor cells by subjecting them to temperature changes or chemical injections. Radiofrequency ablation, or RFA, uses heat to destroy tumors and is most successful when there are fewer than four tumors that are less than 4 centimeters. RFA, which may also be used as a bridge to prepare patients for liver transplant, has a three-year survival rate of up to 85 percent.

Another type of treatment, known as chemoembolization, involves injecting a chemotherapy drug into the hepatic artery, which feeds the tumor with life-sustaining blood, and then tiny particles are used to plug the artery and block blood flow. Chemoembolization has shown only a modest improvement in survival even in patients with the best outlook because the tumor eventually regains its blood supply.

### Hope for Transplant

Improvements in liver transplant offer a bright spot in HCC, say doctors, and more patients may soon become eligible for the procedure.

“The fact that liver transplant has become a real option in the past several years is without question the most exciting and promising thing that has happened for liver cancer patients,” says Goran B. Klintmalm, MD, PhD, chief and chairman of the Baylor Regional Transplant Institute at Baylor University Medical Center in Dallas. “In the past, once a patient had a large liver cancer that couldn’t be removed by surgery, the chance for long-term survival was very poor. But the five-year survival now is 60 percent, versus the 10 percent it used to be.”

At five years, the survival rate for transplant patients is now 60 percent and the risk of recurrence is low at 10 to 20 percent. But two major obstacles prevent broad use of transplant: a lack of suitable donor organs, and few patients are eligible for a transplant because of advanced cancer or the presence of additional

comorbidities that don't involve the liver.

Liver transplant criteria stipulate that ideal candidates either have a single tumor less than 5 centimeters or up to three tumors 3 centimeters or less each in diameter. In recent years, transplant criteria have been the subject of controversy, with some researchers suggesting the criteria be expanded to allow more liver cancer patients to receive transplants while still retaining high success rates. Other experts, however, believe donor livers must be reserved strictly for patients most likely to survive long term.

Many groups set an eligibility cutoff at a projected 50 percent survival at five years. But with liver transplant survival at five years now hovering above that, some experts believe the criteria can be loosened while still maintaining good survival projections.

"There's active discussion about these criteria now, and it's possible we may see a new proposal come out in the spring and perhaps have new criteria implemented in the summer," says Dr. Klintmalm.

Even if the criteria are broadened to include larger or more than three tumors, doctors say the additional group of patients who become eligible is likely to remain small. It's also possible to develop a recurrence of hepatitis infections, which could then ultimately damage the new liver.

Researchers are studying new ways to make more patients eligible for transplant. Dr. Klintmalm and his colleagues are testing a procedure called TheraSphere®, in which tiny glass particles are "loaded up" with radiation and injected into the liver. These particles lodge into the tumor and heavily irradiate it. "We are quite enthusiastic about this," Dr. Klintmalm says. "We do this prior to transplant in hopes of reducing the cancer, making it less aggressive and less likely to come back after transplant."

## Looking to the Future

Bayer and Onyx Pharmaceuticals, makers of Nexavar, are taking steps to file the drug for approval in HCC. A phase III trial testing the effectiveness of Nexavar as a single agent was stopped in February to allow all patients to receive the drug after it was shown to significantly extend survival in patients with advanced HCC. Results of the SHARP trial will be released at the annual meeting of the American Society of Clinical Oncology in early June.

The Food and Drug Administration approved Nexavar, a multikinase inhibitor, in December 2005 for a common type of kidney cancer. The targeted agent works by halting the uncontrolled growth of cancer cells and disrupting the blood supply that feeds the tumor. Results from a phase II study conducted by Dr. Abou-Alfa and colleagues found Nexavar stabilized HCC for a third of the 137 patients in the trial, and 11 patients had some tumor shrinkage. The research, which was published in the *Journal of Clinical Oncology* in September 2006, also uncovered 18 genes that may help doctors predict who would benefit most from Nexavar.

Scientists hope combining Nexavar with chemotherapy will boost efficacy, so a phase II trial is now under way testing Nexavar in combination with Adriamycin.

Avastin® (bevacizumab) is another targeted agent showing moderate benefit in this difficult-to-treat cancer in various combinations with chemotherapy, including Gemzar® (gemcitabine) and Eloxatin® (oxaliplatin). The three-drug regimen resulted in close to half of trial participants having either stable disease or some tumor shrinkage.

Data from a phase II study of Tarceva® (erlotinib), a targeted agent already approved for lung and pancreatic cancer, showed the drug extended median overall survival to more than a year. Unfortunately, none of these new drugs appear to be a homerun for HCC, and researchers continue to examine various targeted agents and drug combinations.

“Liver cancer is a difficult disease,” Dr. Abou-Alfa says. “But we have opportunities both in understanding the biology of it and how molecules talk to each other and make the cancer spread. I think this is considered a hopeful step, and there has been a great effort by many people all over the world.

“But unfortunately, this is not a very well-recognized serious disease, despite the silent epidemic of hepatitis C, and the numbers could be very scary. We need to see more funding and more public interest in liver cancer.”

That’s something John Emerson wanted to see. “I had zillions of things I wanted to do with my friends and places I wanted to go,” Emerson said. “I would just tell other people to do the things they’ve wanted to do and to find resources to help deal with grief and depression. You can get past that and make whatever time you have left quality time.”

Last summer, he went rock climbing at White Horse Ledge, an 800-foot granite slab in the White Mountains of New Hampshire. “I only got half-way up and then I ran out of steam, but I tried it,” he said. Up until his death, he continued to kayak the rapids of the Farmington River in Massachusetts when he felt able, and he got in a little cross country skiing this winter, even if it was just a few feet in his own backyard.

*Editor’s note: John Emerson passed away at his home in Limington, Maine, on February 8, 2007. CURE is proud to honor his memory.*