NEW TECHNOLOGIES
TO TARGET THE RISE IN LIVER CANCER

In March, the National Institutes of Health’s Annual Report to the Nation on the Status of Cancer, 1975-2012 carried the welcome news that cancer rates are falling for most forms of the disease. But the report also included a special section highlighting one exception: “Liver cancer deaths are on the rise in the United States, increasing at the highest rate of all the common cancers during the period 2003-2012.”

“We are just at the beginning of the uptick in liver cancer,” said Jean-Francois (Jeff) Geschwind, MD, Professor and Chair of Radiology and Biomedical Imaging, who has spent two decades researching liver cancer and developing new ways to fight it. “Ten years ago there were 12,000 new cases a year in the United States. Now it’s 28,000.”

Worldwide, the statistics are even more alarming. Only lung cancer kills more people every year than liver cancer. Most of these fatal cases occur in less developed parts of the world. “In Asia and Sub-Saharan Africa, it is a massive problem,” said Dr. Geschwind. “I would not be surprised if, within five years, liver cancer overtook lung cancer.”

About 80-90% of primary liver cancers develop from cirrhosis, a chronic inflammation of the liver. The three main causes of cirrhosis—and therefore the main precursors of liver cancer—are hepatitis B, hepatitis C, and now obesity induced non-alcoholic steatohepatitis (NASH). The World Health Organization estimates that 240 million people have chronic hepatitis B, and 130 to 150 million people have chronic hepatitis C.

“Do the math and you can see how many are going to develop liver cancer,” said Dr. Geschwind. Several new drugs have shown tremendous success against hepatitis C, but are beyond the financial reach of many infected patients.

Liver cancer is mostly asymptomatic in its early phases and often goes undetected until more advanced stages, when surgery is not possible, which explains why survival rates are so poor. And because the patient’s liver is usually severely damaged by cirrhosis as well as cancer, traditional chemotherapy may kill the liver, along with the tumor. “That’s why it’s so critical to treat the cancer only where it actually occurs in the liver,” said Dr. Geschwind, “and to protect as much of the healthy liver tissue as possible.”

That’s the idea behind a therapy called transarterial chemoembolization (TACE). Dr. Geschwind’s research has contributed significantly to it. In TACE, catheters the size of a human hair are loaded with a vehicle consisting of an oily medium or microbeads filled with chemotherapy drugs, usually doxorubicin. Then, with help from sophisticated imaging technology, the catheters are maneuvered via the arterial supply directly into the liver tumor where the vehicle is released, saturating the tumor with chemotherapy over several weeks. Next, other beads are deposited via the same catheter to reduce the arterial inflow to the liver tumor to block the blood flow to the tumor. In essence, TACE simultaneously poisons the tumor while eliminating its blood flow.

“In every other organ,” said Dr. Geschwind, “blood flows in through the artery and out through the vein. But in the liver, 80% of the flow comes from the veins, which brings the blood back from the gut to the liver so the liver can do its job as the body’s chemical factory. Liver tumors, on the other hand, drain
their blood supply almost completely from the artery. So we can exploit this unique property by threading catheters and navigating through the arterial anatomy, thereby targeting the tumor while preserving the healthy liver tissue.”

TACE was pioneered in Japan in the 1980s but didn’t become commonplace in the United States until nearly two decades later. Since then, TACE has steadily improved through advances in drugs, drug delivery, and imaging. Dr. Geschwind has been at the forefront of the research to improve TACE and is one of TACE’s main innovators. He is in the fifth year of a five-year NIH grant that funded research to improve TACE through better imaging, namely “seeing, targeting, treating, and assessing tumor response after therapy.” “By making sure every tumor is visualized, we can ensure that we will never miss the target,” Dr. Geschwind explained.

A specific example of imaging technology that was developed by Dr. Geschwind’s team in collaboration with Philips Healthcare is the ability to visualize the entire liver. This is an especially important problem in the United States where many patients are overweight and therefore performing a cone beam CT scan during a TACE procedure can be challenging. “What we managed to accomplish is to develop software that adjusted the centering process thereby establishing the image rotation around the liver rather than on the patient. This software is now a new commercial product called Open Trajectory.”

To improve the visualization of the liver tumors, Dr. Geschwind’s team developed a dual-phase cone beam CT (DP-CBCT). Unlike earlier methods, it performs two scans from one injection of dye. The first scan reveals the arteries feeding the tumor; these become the pathways used to deliver chemotherapy, which are then blocked off to starve the tumor. The second scan, which is slightly delayed, identifies and visualizes the tumors. After the procedure, another DP-CBCT scan shows how much damage the treatment has done to the tumor. Instead of waiting to learn whether a treatment has worked, both the patient and the care team receive immediate feedback.

To better utilize DP-CBCT, Dr. Geschwind and Philips Healthcare devised software that provides live 3D images to help clinicians navigate through arterial pathways and deliver TACE. “It highlights the roadway to the tumor and calculates the way to get there,” said Dr. Geschwind, “like Google Maps.”

A peculiarity of liver cancer is that even when the tumors respond to treatment, they often don’t shrink. “So we needed a new way of assessing response,” explained Dr. Geschwind. He and his team created yet another software that precisely measures tumor volume and necrosis. Called qEASL, it replaces the usual one- or two-dimensional images with a segmented 3D map of the tumor. Injected dye reveals which parts of the tumor are alive or dead. “So instead of an estimate of the necrosis,” explained Dr. Geschwind, “we have a real number that provides an accurate quantification of tumor kill (70, 80%, etc.) and, as a result, we now have a much better sense of the success of our therapy. We can also determine with greater certainty when re-treatment is not necessary because we know the tumor is dead.”

TACE is now recommended only for patients with intermediate stage liver cancer, but Dr. Geschwind is working on ways to expand its applicability. He wants to use it against more advanced cancers where TACE could be combined with other therapies, such as agents that block the formation of new blood vessels or with immuno-oncology to exploit the profound inflammatory reaction that TACE causes. Here, checkpoint inhibitors could be given simultaneously with TACE or immediately after TACE to unleash the immune reaction. At the other end of the spectrum, patients in need of a liver transplant may be required to wait for a long period of time given the scarce availability of organs. In such cases, TACE is an extremely useful and effective therapy to prevent disease progression, keeping patients eligible to receive a transplant. He recently received another five-year grant from the NIH to pursue his work on TACE, and he has several clinical trials planned or underway at Smilow Cancer Hospital.

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He’s incredibly excited about doing this work at Yale, which recruited him last year from Johns Hopkins. Yale enticed him with the position of department chair and a brand new state-of-the-art lab, not to mention access to world-class facilities at the Positron Emission Tomography (PET) Research Center and the Magnetic Resonance (MR) Research Center. But what sealed the deal was something Dr. Geschwind recognized during the interview process.

“There is something truly special at Yale. The level of enthusiasm and desire to achieve greatness is incredible,” he said. “The people I met during the interview process were amazingly supportive, friendly, and warm. This was true of the other department chairs, the hospital, and medical school leadership. Everyone seemed to be on the same page and functioned in unison like a top class orchestra. I instantly felt like I belonged. I know that we have all the elements to create a Liver Cancer Center of Excellence at Yale. We have top class medical oncology, surgery, transplant, and hepatology. I am absolutely convinced that with the proper support, our center will become the envy of the world.”