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Intraoperative Personalized Radiotherapy: A Pioneering Tool to Treat Complex Cancers

A woman with recurrent colon cancer in the pelvic cavity needed to have treatment to separate areas of her body.

Ravi Kiran, MD, Chief of Colorectal Surgery at NewYork-Presbyterian/Columbia, removed the tumor, but could not cut too close to vital blood vessels and other organs. Because of the limitations of surgery, and because the patient had already received a high lifetime cumulative dose of radiation therapy in previous treatments, Dr. Kiran and **K.S. Clifford Chao, MD**, Radiation Oncologist-in-Chief at NewYork-Presbyterian Hospital, decided to use intraoperative radiotherapy (IORT) to “mop up” any leftover tumor cells. Dr. Chao used a flat radiotherapy applicator to deliver radiation to areas close to blood vessels along the pelvic wall, a spherical applicator to treat a region lower in the pelvic cavity, and a protective wrap, or draping made of material that shields organs such as the bowel or blood vessels from scatter radiation. The patient was recently seen by Dr. Kiran and is doing well, happy with the outcomes.



Dr. Ravi Kiran

“IORT is a new approach to using individualized, internal radiation delivered in the operating room immediately after a cancer tumor is removed,” says Dr. Kiran. “The technique represents an effort to reduce the chance of a recurrence, shorten the duration of conventional postoperative external radiation, and reduce the risk to healthy tissue associated with external radiation.”

Two years ago, NewYork-Presbyterian Hospital became the first hospital in New York City to offer IORT to women with certain breast cancers. In this therapy, a spherical applicator is used to deliver a single, even dose of radiation to the inside surface of a rounded cavity after a lumpectomy.

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A New Era in Gastrointestinal Cancer Therapies

Over the past 25 years, great progress has been made in the management of gastrointestinal malignancies. “I believe that a central theme unifying the progress is innovation in all aspects of cancer therapeutics and management,” says **Manish A. Shah, MD**, Director of Gastrointestinal Oncology, NewYork-Presbyterian/Weill Cornell Medical Center. “We are entering an era of precision medicine, where therapies will be administered based on the genetic profile of an individual’s tumor and not necessarily on its origin. Immunomodulating therapies have shown incredible promise recently. New imaging modalities with novel applications

will change how we see and treat malignancy. And we are also beginning to understand the origins of cancer and cancer stem cells, and how these cancer-initiating cells may be vulnerable.”

A national and international thought leader in gastrointestinal malignancies, Dr. Shah is also Director of the Gastrointestinal Oncology Program at Weill Cornell Medical College. Here, he and his colleagues pursue clinical and translational research that focuses on drug development and improving the treatment of cancers of the upper and lower gastrointestinal tract.

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A New Era in Gastrointestinal Cancer Therapies

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A Rise in Early Onset Colon Cancer

While the incidence and mortality of colorectal cancer in the general population has declined significantly in the last decade, not all age groups have seen a decrease, specifically among those 20 to 50 years old. “The rise in cancer incidence in this particular population is concerning, yet there is no in-depth characterization of these patients, their tumors, or how they differ from patients who develop cancer over the age of 50,” says Dr. Shah. “Because of clinical differences observed, we have hypothesized that there is an underlying molecular difference in early onset colon cancers.”

To this end, Dr. Shah, Heather Yeo, MD, and Emily Zheng, PhD, are analyzing the National Cancer Institute’s SEER (Surveillance, Epidemiology, and End-Results) database to characterize the clinical and pathologic differences between patients with early onset colorectal cancer and the traditional group of patients over 50. Working with Doron Betel, PhD, and Rhonda Yantiss, MD, Dr. Shah is also using colon and rectal cancer data from the Cancer Genome Atlas to examine the genomic differences between these two populations.

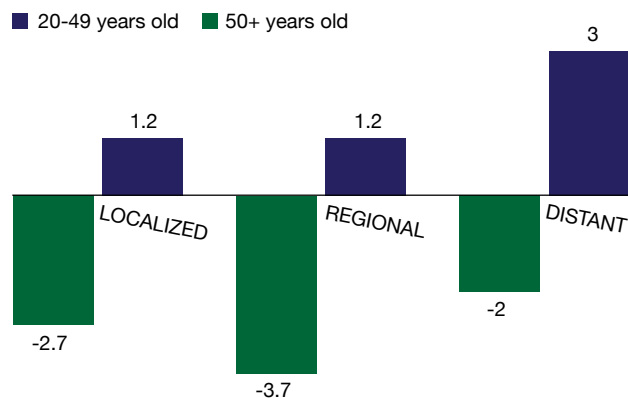


Dr. Elizabeta C. Popa, Dr. Manish Shah, and Dr. Tong Dai

“The message here is that early onset colon cancer is rising in the United States and we are trying to understand the molecular reasons for that,” says Dr. Shah. “We think it may be very similar to reasons in the Chinese population, or other populations like in Saudi Arabia, so we are addressing it from a more global perspective. This is important because we live in an increasingly global community. We see many patients from the Middle East. There are many Chinese Americans in New York City as well as in the Northeast.”

Temporal Trend of Incidence

Young vs Old Onset Colorectal Cancer by Location
Annual Percent Change - 2000 to 2011



Source: SEER, 2000-2011

“We know that younger patients have more aggressive biology in the progress of the disease, as well as a poorer prognosis,” says **Tong Dai, MD, PhD**, who joined the Solid Tumor Service in the Division of Hematology and Medical Oncology at NewYork-Presbyterian/Weill Cornell in 2014. In order to further this understanding of the role of genetic factors, the Weill Cornell Gastrointestinal Oncology group is planning a joint study of early onset colon cancer with colleagues at Fudan University Medical College and Cancer Hospital in Shanghai. This study will use whole genome sequencing in order to determine if there are any genetic mutations that predispose the development of colon cancer in younger people.

“Colon cancer and other gastrointestinal cancers are highly prevalent in China,” notes Dr. Dai. “Our colleagues at Fudan University will collect tissue samples and process the DNA sequencing of patients with early onset colon cancer, and we will provide help in interpreting the data. Once we identify potential significant genes, we will continue the work at Weill Cornell, including introducing the mutation into colon cancer cell lines to see if it alters the growth pattern of the cancer cells and makes them more aggressive. We also plan to test available inhibitors to see if there is any therapeutic utility for those mutations.”

Therapeutic Challenges: Elevating the Standard of Care in Anal Cancer and Primary Liver Cancer

Elizabeta C. Popa, MD, Assistant Professor of Clinical Medicine, Gastrointestinal Oncology Group, is actively involved in clinical trials as principal investigator and co-investigator in the areas of hepatobiliary cancers and anal cancer. In addition to her work in difficult-to-treat, locally advanced, and metastatic gastrointestinal disease, she has particular interest in “underdog” cancers – including anal cancer and primary liver cancer – that are either resistant to many of the available drugs or that affect a small percentage of the population.

“Squamous cell carcinoma of the anus is about the sixth or seventh most common of GI cancers,” says Dr. Popa. “While its incidence is relatively low in the U.S., Weill Cornell is located in a large metropolis, where there is a relatively higher concentration of cases. This has brought this disease to our attention. Our group rapidly realized the dire need for more treatment options for patients with disease that is not localized or amenable to chemoradiation therapy either in the first line or recurrent setting.

“Currently there are very few therapies for advanced anal cancer,” says Dr. Popa. “Now, in 2014, we are basically stuck with the treatment options that have been the same for the past 30 years. However, we have had some fortuitous discoveries when treating patients with advanced disease who have exhausted standard platinum-based chemotherapy. Based on our current knowledge of molecular signatures that drive squamous cell carcinomas in general, we used a well-studied regimen that is in standard use for colorectal cancer and noted a remarkable response in our patients with metastatic anal cancer. We then noted that several other reports of similar benefits were reported as case reports by other investigators worldwide. We are now poised to open an investigator-initiated clinical trial exploring this regimen with prospective molecular marker analyses to identify disease markers, as well as determinants of response and overall outcomes. Our study would be

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A New Era in Gastrointestinal Cancer Therapies *(continued from page 2)*

one of very few trials in the country specific for metastatic or locally advanced anal and squamous cell anal cancer.

"We don't just want to keep 'borrowing' regimens from other cancer types. In this era of increasingly individualized cancer treatment we want to increase our understanding of the mechanisms driving this disease," says Dr. Popa. "As we gather data for gene expression and response rates in this trial, we can then further tailor upcoming second and third generation trials to exploit new targeted therapies, which are being developed in the pharmaceutical industry.

"While there is a paucity of options for anal cancer, we may be overtreating certain rectal cancer patients," continues Dr. Popa. "Weill Cornell is also participating in a national study of neoadjuvant therapy in patients with localized rectal cancer. In an attempt to de-escalate potentially unnecessary and toxic therapy, this trial aims to see if we can forego radiation therapy in these patients." Patients will be randomized to receiving chemoradiation or not [currently the standard of care for all patients with stage III disease] based on the radiologic response to neoadjuvant chemotherapy as measured by preoperative PET scan imaging.

"In liver cancer treatment, early or limited extent disease has several therapeutic options, including surgical removal, organ transplantation, or loco-regional therapies such as ablation or embolization," says Dr. Popa. "However, in extensive or advanced disease, liver cancer has been largely resistant to traditional cytotoxic chemotherapy agents and treatment options are very limited."

With the advent of targeted therapies, only one standard of care therapy – Nexavar® – has emerged. "By itself, Nexavar is of limited benefit, and though it is an oral agent that represented a breakthrough for this disease, it is often very difficult to tolerate by patients," says Dr. Popa. "We are now participating in two clinical trials for treatment of locally advanced or metastatic liver cancer looking at Nexavar in combination with other agents in the hope of providing more effective and more numerous therapeutic options."

Weill Cornell is participating in a large national multicenter trial that is testing Nexavar along with the chemotherapeutic agent, doxorubicin. Another trial, which is a collaborative, industry-sponsored trial that is open at only a few academic centers nationwide combines Nexavar with a novel oral TGF-beta inhibitor. "In general, the molecular target of therapies against liver cancer has been neoangiogenesis," says Dr. Popa. "Current novel therapies such as the one being tested in our TGF-beta inhibitor trial are attempting to target new ways of disrupting tumor growth, as well as tumor blood vessel formation.

"At the end of the day, what permits patients with metastatic malignancy of any type to have an increased survival is the number of lines of therapy available," says Dr. Popa. "As an example, nowadays there are many more lines of effective therapy for colorectal cancer than ever before. This has translated into a potential for years of survival with metastatic disease. In both anal and liver cancer we need more lines of therapy and thus more weapons to fight the disease and offer better outcomes for our patients."

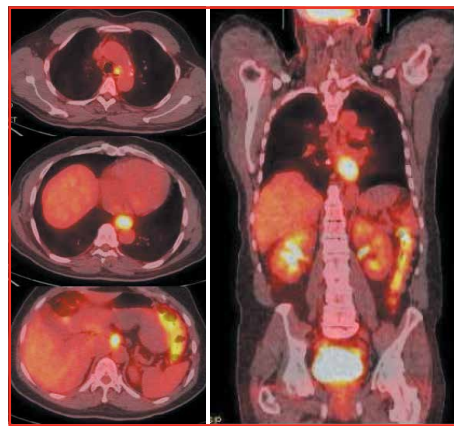
The Role of PET Imaging in Tracking Treatment

Cancers of the upper gastrointestinal tract (esophagus, gastric, and pancreatic cancers) form a highly morbid group of malignancies, with the mean survival for patients being less than one year. While much has been achieved in therapeutic strategies, the vast

majority of newly diagnosed patients with these cancers will die of their disease.

Drs. Shah, Dai, and Popa recently published the results of their study on the role of ^{18}F -FDG PET (^{18}F -fluorodeoxyglucose positron emission tomography) for identifying metastatic disease in the upper gastrointestinal tract in *Current Treatment Options in Oncology*. The uptake of ^{18}F -FDG by tissues is a marker for the tissue uptake of glucose, which in turn is closely correlated with certain types of tissue metabolism. After ^{18}F -FDG is injected into a patient, a PET scanner can form two-dimensional or three-dimensional images of the distribution of ^{18}F -FDG within the body. "While its use is prevalent in the United States, ^{18}F -FDG PET is underutilized worldwide, especially in countries with a growing emergence of gastroesophageal cancers, despite the evidence of clear benefit in cancer staging, and in some cases, response assessment and surveillance," notes Dr. Shah. "FDG is a radioactive form of glucose

that accumulates in cancer cells," continues Dr. Shah. "There has been a fair amount of work looking at how FDG PET imaging is useful to better stage tumors and to identify occult metastases or when a recurrence happens after surgery. A newer area of application



PET imaging of esophageal squamous cell carcinoma

is being able to identify early, perhaps after one or two treatments, if there is a response to treatment. If the uptake of glucose is diminished very early within the first month of treatment, you might see a change in the glucose uptake before you see a size change on a CT scan."

The researchers concluded that the use of PET-based imaging is a rapidly evolving field with new radiolabeled agents in design and under investigation. "The rational design of imaging systems using knowledge gained about cellular biology and metabolism will hopefully allow us to have malignancy-specific imaging tailored to specific biologic behaviors," says Dr. Shah. "Continued work on the use of PET imaging will allow routine assessment of therapeutic response in the neoadjuvant setting, with the possibility of formulating individualized treatment plans with the availability of accurate prognostic determination based on pretreatment imaging."

Most recently, the Weill Cornell researchers received approval to lead a national trial through the National Cancer Institute's Alliance for Clinical Trials in Oncology that tests whether an early PET scan could change the course of therapy, and if changing therapy could improve outcomes. "Our aim is to better refine the use of a PET scan," adds Dr. Shah. "Sometimes physicians will order a PET scan early to see if things are working or not working, but if you can't act on it you have to ask if it's valuable."

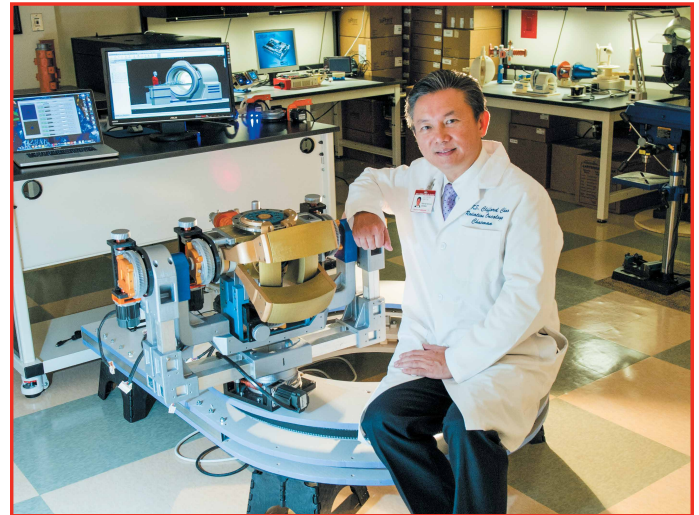
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Intraoperative Personalized Radiotherapy: A Pioneering Tool to Treat Complex Cancers *(continued from page 1)*

Now physicians at NewYork-Presbyterian/Columbia are expanding the use of IORT to cancers in the abdomen and pelvis. Unlike that in the breast, the tumor bed in the abdomen and pelvis may not be as clearly defined after surgery, and several sites at risk for recurrence may need to be treated. “When you’re performing an operation dealing with complex cancers, the general principle is to remove it with clear margins on all sides,” says Dr. Kiran. “However, removing a tumor from the liver, bowel, or pancreas with clear margins is challenging because the terrain of the surgical bed is more uneven, unlike the inside surface of a rounded cavity after a lumpectomy. If the tumor is recurrent, in an awkward position where a surgeon doesn’t have much room to maneuver, or if it is attached to other structures then chemotherapy or radiation is often recommended before or after surgery.”

However, as Dr. Kiran points out, many of these patients have already received radiation several times and, therefore, have reached the maximum dose. Giving them more external radiation to destroy the microscopic cancer cells left behind could damage the “innocent bystander” cells. “These patients still require therapy that reduces the possibility of the cancer recurring,” says Dr. Kiran. “This is where IORT can be particularly effective. With IORT, risks of excessive radiation to the patient are minimal because we can deliver a very focused dose through contact radiotherapy. Portable IORT equipment fits easily into an operating room, allowing both the surgeon and radiation oncologist to deliver the radiation therapy without the need to transport the patient to another operating room.

“By performing the procedure in the OR, you can directly place the device right next to the targeted area,” says Dr. Kiran. “The radiation only travels a very short distance to the localized section so that it doesn’t damage surrounding structures even though it delivers a high amount of radiation. IORT can also reduce the duration of any postoperative external radiation.”



Dr. K.S. Clifford Chao

Currently, Dr. Chao is working with engineers and physicists from NewYork-Presbyterian to design and develop applicators for colorectal, head and neck, lung, and gynecologic cancers. “We need radiotherapy applicators that suit the specific anatomical terrains,” says Dr. Chao. “In some areas of the body, the applicator could be a half sphere, an irregular shape for uneven surfaces, or a tiny device that fits into a small space where we have anatomic challenges. We can devise personalized therapy based on a patient’s specific anatomy.”

“For patients with these advanced cancers, IORT offers us a potential for cure,” says Dr. Kiran.

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A New Era in Gastrointestinal Cancer Therapies *(continued from page 3)*

Discussing Bevacizumab for Noncolorectal GI Malignancies

The Weill Cornell researchers have also recently published the results of their investigation of bevacizumab – a potent inhibitor of vascular endothelial growth factor A that has demonstrated modest anti-tumor activity across a broad range of malignancies when combined with chemotherapy. “In colorectal cancer, bevacizumab in combination with chemotherapy is a standard of care for first-line therapy and is used as second-line therapy in both bevacizumab-naïve patients and those who have progressed on first-line therapy containing bevacizumab,” says Dr. Shah.

Bevacizumab has been examined in nongastrointestinal malignancies as well, and across multiple studies – virtually all of which demonstrate some improvement in progression-free survival – the combination of chemotherapy and bevacizumab has not led to a significant improvement in overall survival. “Unfortunately, the addition of bevacizumab to chemotherapy translates into only slight improvement in overall survival in a few malignancies, including colorectal cancer,” he says. In his review, Dr. Shah highlights the development of bevacizumab in noncolorectal gastrointestinal malignancies and potential directions in antiangiogenic drug development.

“The questions that we are trying to answer in each of these diseases are what is the biology that is driving the disease and is there a therapeutic advantage we can achieve by understanding that disease biology,” adds Dr. Shah. “It’s an exciting time to be an oncologist because there are many new drugs and many pathways to attack. How to do it properly will change how we treat cancer in the future.”

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Addressing Pre- and Post-Liver Transplant Virological Response in Patients with Hepatitis C

Chronic hepatitis C virus (HCV) infection affects more than three million Americans and is a major cause of liver disease, cirrhosis, and liver cancer, and it is also the most common indication for liver transplantation. Treatment of HCV before and after a patient receives a liver transplant is a major focus of study by **Robert S. Brown, Jr., MD, MPH**, Director, Center for Liver Disease and Transplantation, NewYork-Presbyterian/Columbia University Medical Center, and his colleagues.

“Previously, the treatment of hepatitis C in the period just before transplantation was impossible,” says Dr. Brown. “Patients could have been treated in the distant past before they needed a transplant, but once a patient’s liver thickened to the point that they needed transplantation, we had two problems.

Number one, the therapy we used didn’t work as well since the response rates going from mild liver disease to cirrhosis got worse. Going from milder forms of cirrhosis to more advanced forms of cirrhosis, and needing transplantation, they got even worse. Add to that the fact that when patients had more advanced cirrhosis, they couldn’t tolerate interferon, which had been the backbone of hepatitis C therapy since 1991.”

Interferon was successful in some individuals but also quite toxic and many patients could not tolerate the side effects, explains Dr. Brown. “Even among those who started therapy, only about two-thirds to three-quarters could finish it,” he says. “That did not include many other individuals who didn’t start therapy because either their perception or their physician’s perception was that they couldn’t tolerate it. And almost no patients with advanced cirrhosis could tolerate it.”

Dr. Brown stresses that unlike hepatitis B and HIV, hepatitis C is curable. “It is an RNA virus – it doesn’t go into the nucleus of the cell, and if the virus doesn’t make copies of itself it dies,” he says. “That is something that took us a long time to realize. If the virus isn’t detected three months after a patient has finished therapy, it is more than 99 percent likely that the person is forever cured. And unlike HIV, hepatitis B, or even chicken pox, which can come back later as zoster, there does not seem to be hidden



Dr. Robert S. Brown, Jr.

reservoirs of hepatitis C in the liver in those 99 percent plus of people.”

In virtually all of the cases, says Dr. Brown, “if patients went into transplant with the virus present, they came out of transplant with the virus present. However, we learned that even with short courses of therapy, if the virus was negative in their blood when they went into the transplant and then the liver was removed, most would be cured. According to Dr. Brown, if HCV was removed from the blood prior to transplant – even for a short time – the virus did not return. “When we had our first successful all-oral therapy, which was sofosbuvir and ribavirin, we saw the same thing. You could use a shorter course of sofosbuvir and ribavirin, clear the blood of HCV for four to six weeks, perform the liver transplant, and the patient seemed to be cured.”

Post-transplant some individuals could take the interferon-based therapy because they no longer had cirrhosis of the liver, but, says Dr. Brown, “the response rates were much lower because the patients were immunosuppressed and did not tolerate the interferon very well.”

Dr. Brown and his colleagues have continued to focus research on active antiviral regimens for hepatitis B and C and have been pursuing several multicenter studies to investigate anti-viral prophylaxis strategies, as well as various immunosuppressive agents, following liver transplantation.

Most recently the results of one of these studies aimed at evaluating the safety and efficacy of NS3/4A protease inhibitor (PI)-based triple therapy in patients awaiting liver transplant was published in the June 2014 issue of *Liver International*.

Patients treated with triple therapy pre-liver transplant from two centers were prospectively enrolled in an observational cohort. The investigators sought a 12-week sustained virological response as the primary outcome; pre- and post-liver transplant virological response rates and safety were secondary outcomes.

Twenty-nine patients were treated with telaprevir or boceprevir-based triple therapy for a median range of 27 weeks. Twelve patients underwent liver transplant, 75 percent with undetectable viral load. The overall sustained viral response rate at 12 weeks (SVR12) was 52 percent, including pre-liver transplant SVR12 of 41 percent in patients who completed treatment and follow-up on the wait list, and the post-liver transplant virologic response (pTVR12) of 67 percent among transplanted patients. The pTVR12 rate was 89 percent among those patients with undetectable viral load at liver transplant.

The study concluded that overall SVR12 and pTVR12 rates are high among patients treated with PI-based triple therapy while awaiting liver transplant, even in this difficult-to-treat population. However, they note that caution is needed as early discontinuation and serious adverse events are common.

“We still don’t know if we can use these drugs in patients who have very thick livers who are awaiting transplant,” says Dr. Brown. “These newer drugs that have just gotten FDA approval are now being used for post-transplant when the liver is healthy again. However, they can’t be used to treat and cure people pre-transplant, which would obviously prevent post-transplant problems, or one would hope, in some cases, stabilize the liver to prevent or delay the need for a liver transplant. That research, which we are also conducting with different combinations of drugs, is ongoing.

“The first Holy Grail is to be able to cure hepatitis C in the majority of patients,” continues Dr. Brown. “We think we’re on the brink of that with these two new drugs.”

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Advances in Gastroenterology and GI Surgery

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Addressing Pre- and Post-Liver Transplant Virological Response in Patients with Hepatitis C (continued from page 5)

Dr. Brown also notes that there are eight to 10 drugs currently in the late stages of development that will be approved over the next year. “The hope is that we will have a drug regimen for every patient with hepatitis C,” he says. “I think we are very close to the point where we are going to have therapy to treat all patients. The question that we’re still investigating is that none of these therapies has been tested in patients with very thick livers – the patients who are on the transplant waiting list. In that group

of patients we don’t know if these drugs are safe or effective, but even more importantly, if these therapies will stabilize the liver and eliminate the need for liver transplantation.

“Where we would ultimately like to be is where everybody gets cured pre-transplant,” adds Dr. Brown. “We would like for all patients to get better after being treated so that they don’t need a transplant, but that’s a long way off.”

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