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Marc Bessler, MD
Chief, Minimal Access/
Bariatric Surgery
NewYork-Presbyterian/
Columbia University
Irving Medical Center
mb28@cumc.columbia.edu

David E. Cohen, MD, PhD
Chief, Gastroenterology
and Hepatology
NewYork-Presbyterian/
Weill Cornell Medical Center
dcohen@med.cornell.edu

Jeffrey W. Milsom, MD
Chief, Colon and Rectal Surgery
NewYork-Presbyterian/
Weill Cornell Medical Center
mim2035@med.cornell.edu

Timothy C. Wang, MD
Chief, Digestive and Liver Diseases
NewYork-Presbyterian/
Columbia University
Irving Medical Center
tcw21@cumc.columbia.edu

Redefining Selection Policies for HCC Liver Transplantation

Karim J. Halazun, MD, a hepatobiliary and liver transplant surgeon in the Center for Liver Disease and Transplantation at NewYork-Presbyterian/Weill Cornell Medical Center, has sought ways to improve and optimize the current liver transplantation allocation system. In the October 2018 issue of the *Annals of Surgery*, he served as lead author in a bicoastal collaboration to redefine hepatocellular carcinoma (HCC) liver transplantation policies.

In describing the current landscape of organ allocation for HCC, Dr. Halazun shares a historical perspective. "Thomas Starzl, the father of liver transplant in the 1960s, thought that liver transplantation was the best cure for liver cancers like hepatocellular carcinoma. Unfortunately, in the 70s and 80s that led to transplanting every single person with liver cancer who came through the door, so the outcomes weren't great. In the mid to late 80s,

Dr. Karim J. Halazun

there were such high recurrence rates that it was decided transplant was too high risk and that this was not the best approach for these patients."

In 1996, Vincenzo Mazzaferro in Milan, Italy, published a paper in *The New England Journal of*

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A New Pancreatitis Program: Comprehensive Care for Progressive Pancreatic Disease

The management of acute and chronic pancreatitis requires the skills and expertise of medical and surgical gastroenterology specialists who can offer patients a wide range of treatment modalities. "Pancreatitis can be a difficult disease entity to treat," says **John M. Poneros, MD**, Medical Director of the newly established Pancreatitis Program at NewYork-Presbyterian/Columbia University Irving Medical Center. "These patients can experience episodes of chronic pain or intermittent severe attacks of pancreatitis requiring hospitalization. They can also be understandably anxious about getting their next attack or whether or not they're at risk for cancer. Given our experience and the enormous volume of patients with pancreatic disease that we see here at Columbia, we felt that it was valuable to formalize our treatment of these patients with a full-service program."

> "Given our experience and the enormous volume of patients with pancreatic disease, we felt that it was valuable to formalize our treatment of these patients with a full-service program."
> — Dr. John M. Poneros

With funding from the Diller-von Furstenburg Family Foundation, the Pancreatitis Program, part of Columbia's Pancreas Center, launched in

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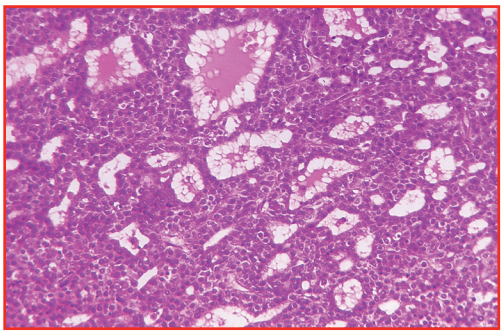
Redefining Selection Policies for HCC Liver Transplantation (continued from page 1)

Medicine defining criteria to select patients. The Milan criteria set clear guidelines for which patients with HCC benefit from transplant with an acceptable recurrence-free survival. These criteria were adopted globally by several transplant authorities to prioritize or even preclude liver transplant for patients with HCC.

"The Milan criteria include a single tumor less than or equal to 5 cm, or up to three tumors, none of which are larger than 3 cm," says Dr. Halazun. "If the patient is within those criteria, the recurrence free survival rate approaches 90 percent at five years. Basically, those criteria were based on 35 patients in Milan. It was a small sample size, but the impact was enormous."

According to Dr. Halazun, before the Milan criteria were adopted in 2002, 2 percent of liver transplants were done for HCC – about 1,500 to 2,000 transplants. Since then, about a third – 30,000 out of 90,000 adult transplants – have been performed for HCC. "It's a huge shift in volume because of these criteria and because the outcomes are so good," he says. "These patients are also relatively easy to transplant, and they do well."



Hepatocellular carcinoma

The Model for End-Stage Liver Disease, or MELD, a scoring system for assessing the severity of chronic liver disease, is now used by the United Network for Organ Sharing (UNOS) for prioritizing allocation of liver transplants. As Dr. Halazun explains, "Patients with HCC don't have high MELD scores, so they are given an 'exception' score based on if they are within these criteria. They start at 28 points and ultimately go up to a cap of 34 points. In some parts of the country, that means they get transplanted as soon as they get on the list and are given the points. In New York it means that patients can wait nine months to a year to get transplanted. The questions we asked were: 1) Are we giving them too much priority and 2) Are we excluding patients who have tumors that are outside these criteria? What we found (in a previous publication) is that patients who waited longer actually did better, which is counterintuitive from a cancer standpoint. As a result, UNOS changed its policy to implement a six-month waiting rule at which time points are assigned."

A Bicoastal Collaboration

Dr. Halazun and his colleagues began to look at redefining the criteria, and, indeed, they were not alone in this endeavor.

"There have been many papers that showed the Milan criteria are not the best way to select patients – even the author of Milan has suggested several other criteria," says Dr. Halazun, who in 2018 joined in this effort with liver transplant colleagues at NewYork-Presbyterian/Columbia, Mount Sinai Medical Center, and the David Geffen School of Medicine at UCLA.

According to the investigators, despite the utility and reproducibility of the Milan criteria, they have been criticized for their restrictiveness, and more importantly, for the lack of tumor biological indices to help dictate best oncological practice when transplanting HCC patients.

Using Serial AFP to Predict Outcomes

Dr. Halazun and the research team developed criteria that include tumor biological indices, such as alfa-fetoprotein (AFP), to predict outcome. "AFP has long been recognized as a biological predictor of prognosis in HCC and has been central to many of the new models developed for the transplant setting," says Dr. Halazun. "Unfortunately, many systems have used AFP at a single time point even though patients usually wait many months for transplantation during which time neoadjuvant therapies are administered."

> "What we found with this study is that incorporating AFP response is not only predictive of outcome, but it tells us who we should include who are outside of the criteria that would have very good survival."
>
> — Dr. Karim J. Halazun

The researchers hypothesized that the response of AFP over time serves as a better predictor of recurrence and survival and sought to investigate the importance of a dynamic AFP response through their study of 1,450 adult patients undergoing liver transplant for HCC between January 2001 and December 2013 at NewYork-Presbyterian, Mount Sinai, and UCLA. AFP response was measured as differences between maximum and final pre-liver transplant AFP.

The researchers concluded that "incorporating AFP response over time into HCC selection criteria allows for the expansion of the Milan criteria. As UNOS considers adding AFP to selection algorithms, the NYCA score provides an objective, user-friendly tool for centers to appropriately risk-stratify patients."

"What we found with this study is that trending AFP is not only predictive of outcome, but it tells us who outside of the criteria would have very good survival. These are people who would traditionally not get transplanted in many centers but who actually could be transplanted," says Dr. Halazun. "If they had been transplanted, they would have had upwards of a 70 percent five-year recurrence-free survival."

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A New Pancreatitis Program: Comprehensive Care for Progressive Pancreatic Disease (continued from page 1)

Dr. John M. Poneros

Dr. Beth A. Schrope

2018 under the leadership of Dr. Poneros and **Beth A. Schrope, MD, PhD**, Surgical Director. As a major referral center for other hospitals, the Columbia team frequently accepts patients with complex disease requiring tertiary care. "We're able to offer multidisciplinary care for these patients that is not as easily available at other institutions, for example, a patient with necrotizing pancreatitis who requires invasive treatment, or a patient with a fever who is not responding to antibiotics and has a significant amount of inflammation in their abdomen," says Dr. Poneros. "We're able to accept these patients for transfer and help provide a better outcome."

The program offers minimally invasive treatment approaches that include endoscopic cystogastrostomy and endoscopic necrosectomy for patients that previously would have undergone open surgery in order to remove infected necrotic tissue.

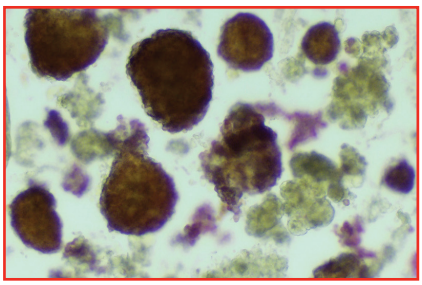
In addition to the latest medical, endoscopic, and surgical treatments, and nutritional support, genetic testing is available for patients with idiopathic recurrent acute pancreatitis. "With genetic testing and cutting-edge endoscopic imaging capabilities, we're able to go that extra mile in figuring out whether there's an intervenable etiology to their pancreatitis," explains Dr. Poneros. "Often there will be an unrecognized mutation that might be contributing to the patient's symptoms. We also convene a weekly multidisciplinary conference to review all of our complicated pancreatic cases, which is attended by surgeons, radiologists, oncologists, radiation oncologists, and other pancreatologists."

When Surgery is Necessary: Total Pancreatectomy and Auto Islet Transplantation

"My philosophy is that surgery for chronic pancreatitis is the last stop," says Dr. Schrope, who is among some 20 surgeons in the country – and who was the first in Manhattan – to perform total pancreatectomy with autologous islet cell transplantation. "I recommend surgery only after other nonsurgical therapies have been exhausted. Nutritional management and endoscopic therapies can be very useful in patients with this disease. I want all of these things to have been tried prior to considering surgery, and then my approach is as long as we can relieve the patient's pain, let's keep as much of the pancreas as possible."

Total removal of the pancreas results in the likely development of diabetes. During the pancreatectomy, the surgical team removes the pancreas, isolates the insulin-secreting islet cells, and then injects the islet cells into the patient's liver, where, hopefully, they take root and continue to produce insulin. "Removing the whole pancreas significantly improves or even eliminates the pain in over 90 percent of patients who undergo the procedure," says Dr. Schrope. "And, while islet cell transplantation may enable the patient to continue producing isulin, the procedure is not always successful. A third of patients will make some insulin, but they will still need to take insulin. Another third will be insulin free for some time – four years, seven years, 10 years – but eventually the islets will fail and then the patients will become diabetic. But one-third of the time the procedure won't work at all – the pancreas has been too damaged, the islet cells don't engraft, and the patients don't make any insulin appreciably."

Dr. Schrope tries to perform a surgery that is short of a total pancreatectomy, if possible. "Can I take only part of the pancreas," she asks, "or can I just reroute the pancreas depending on what the anatomy looks like so that we can save the pancreas to keep those islets working."



Hematoxylin and eosin stain of sample from islet chamber. Free islets are dark red; acinar tissue debris is lighter yellow.

Dr. Poneros and Dr. Schrope collaborate on the treatment plan of each patient, taking into account the etiology of the pancreatitis when recommending specific therapies. "If it's due to alcohol and you know that the patient has stopped drinking, hopefully they won't get any more pancreatitis and there's no need to operate," says Dr. Schrope. "Sometimes it's a sequella of one very bad attack of acute pancreatitis from gall stones that results in scarring of the pancreas. There is also autoimmune pancreatitis, a rare entity thought to be caused by the body's immune system attacking the pancreas. Hyperlipidemia is another cause."

Of all the patients for which Dr. Schrope has performed total pancreatectomy and auto islet transplantation, hereditary pancreatitis is a factor in about 30 percent. "In certain types of genetic pancreatitis there is a significantly increased risk of getting pancreatic cancer, so we work that into our treatment plan," she says. "If the patient has the PRSS1 gene defect, for example, there is about a 10-fold increased risk of pancreatic cancer. Even before islet cell therapy became popular, we would remove the pancreas in these cases to avoid pancreatic cancer in the future. And now with islets, as long as we're fairly reassured that the patient has a benign disease, we can take

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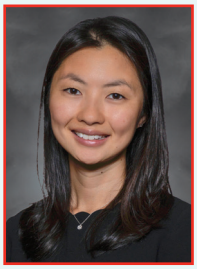
Major Faculty Expansion in Gastroenterology and GI Surgery (continued from page 5)

Gastroenterology

Ravi Sharaf, MD, MS
Gastroenterology and Hepatology
NewYork-Presbyterian/Weill Cornell
(212) 746-4014 • ras9030@med.cornell.edu

- Clinical cancer genetics
- Hereditary GI cancer syndromes
- Health services research

Hepatology



Elizabeth X. Zheng, MD
Digestive and Liver Diseases
NewYork-Presbyterian/Columbia
(212) 305-0914 • exz2001@cumc.columbia.edu

- Acute and chronic liver disease
- Liver cancer
- Transplant hepatology

Surgery

Debbie Bakes, MD
Colorectal Surgery
NewYork-Presbyterian/Columbia
(212) 342-1155 • db3023@cumc.columbia.edu

- Laparoscopic, robotic and minimally invasive colorectal surgery
- Management of anorectal conditions
- Management of pelvic floor disorders

Brendan M. Finnerty, MD
Endocrine Surgery
NewYork-Presbyterian/Weill Cornell
(212) 746-5130 • bmf9002@med.cornell.edu

- Endocrine and neuroendocrine surgical oncology
- Minimally invasive surgery
- Robotic surgery

Daniel P. Geisler, MD
Colorectal Surgery
NewYork-Presbyterian/Columbia
(212) 342-1155 • dpg2122@cumc.columbia.edu

- Minimally invasive colorectal surgery
- Multimodality treatment of low and unfavorable rectal cancers
- Least-invasive surgery for ulcerative colitis

Deborah S. Keller, MD
Colorectal Surgery
NewYork-Presbyterian/Columbia
(212) 342-1155 • dsk2101@cumc.columbia.edu

- Anorectal procedures
- Laparoscopic, robotic and minimally invasive colorectal surgery
- Colonoscopy
- Management of pelvic floor disorders

J. Mark Kiely, MD
Colorectal Surgery
NewYork-Presbyterian/Columbia
(212) 342-1155 • jmk2270@cumc.columbia.edu

- Robotic rectal cancer surgery
- Crohn's disease and inflammatory bowel disease
- Sphincter-sparing anal fistula surgery

A New Pancreatitis Program: Comprehensive Care for Progressive Pancreatic Disease (continued from page 3)

out the pancreas and give the patient their islet cells at least to try to avoid the diabetes."

"We're realizing that we need to be aggressive with progressive pancreatic disease, rather than accepting the notion that there's not much to offer these patients in terms of stopping the march to chronic pancreatitis and potentially pancreatic cancer," adds Dr. Poneros. "Our goal is to intervene to help stem that tide, whether it's endoscopically, medically, surgically, or one day, genetically. We want referring physicians to know that we have the resources and the expertise to help them manage these very challenging patients."

Reference Articles
Guo A, Poneros JM. The role of endotherapy in recurrent acute pancreatitis. *Gastrointestinal Endoscopy Clinics of North America.* 2018 Oct;28(4):455-76.

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For More Information
Dr. John M. Poneros • jmp14@cumc.columbia.edu
Dr. Beth A. Schrope • bs170@cumc.columbia.edu

Major Faculty Expansion in Gastroenterology and GI Surgery

NewYork-Presbyterian/Weill Cornell Medical Center and NewYork-Presbyterian/Columbia University Irving Medical Center have enhanced the breadth and depth of their gastroenterology, hepatology, and GI surgery programs with the appointment of new faculty who bring a wide range of experience and expertise in multiple specialties.

Gastroenterology

Andrea Betesh, MD
Gastroenterology and Hepatology
NewYork-Presbyterian/Weill Cornell

(646) 962-5308 • anb9279@med.cornell.edu

- Hereditary GI cancer syndromes
- Gastrointestinal cancers
- General gastroenterology

Jennifer Caceres, MD
Digestive and Liver Diseases
NewYork-Presbyterian/Columbia

(212) 932-4534 • jc4874@cumc.columbia.edu

- General gastroenterology
- Liver disorders
- Video capsule endoscopy

Akash Goel, MD
Gastroenterology and Hepatology
NewYork-Presbyterian/Weill Cornell

(646) 962-4000 • akg9005@med.cornell.edu

- General gastroenterology
- Nutrition and integrative health
- Obesity and weight management

Susana Gonzalez, MD
Gastroenterology and Hepatology
NewYork-Presbyterian/Weill Cornell

(212) 746-4014 • sug9009@med.cornell.edu

- Gastroesophageal disorders
- Gastrointestinal cancers
- Pancreas disorders

AnnMarie Kieber-Emmons, MD
Gastroenterology and Hepatology
NewYork-Presbyterian/Weill Cornell

(646) 962-4000 • alk2059@med.cornell.edu

- Hereditary GI cancer syndromes
- Gastrointestinal cancers
- General gastroenterology

Dana J. Lukin, MD, PhD
Gastroenterology and Hepatology
NewYork-Presbyterian/Weill Cornell

(212) 746-5077 • djl9010@med.cornell.edu

- Crohn's disease
- Ulcerative colitis
- Pediatric IBD transition care

SriHari Mahadev, MD, MS
Gastroenterology and Hepatology
NewYork-Presbyterian/Weill Cornell

(646) 962-2382 • srm9005@med.cornell.edu

- Advanced endoscopy
- Early esophageal, gastric, and colonic neoplasms
- Pancreatic and biliary disease

Saurabh Mukewar, MB, BS
Gastroenterology and Hepatology
NewYork-Presbyterian/Weill Cornell

(646) 962-2382 • mss9022@med.cornell.edu

- Advance endoscopy
- Cancer of the liver, bile duct, and pancreas
- Polyps and subepithelial lesions

Carolyn Newberry, MD
Gastroenterology and Hepatology
NewYork-Presbyterian/Weill Cornell

(646) 962-4000 • can9054@med.cornell.edu

- General gastroenterology
- Obesity and weight management
- Nutritional disorders and food intolerances

Kartik Sampath, MD
Gastroenterology and Hepatology
NewYork-Presbyterian/Weill Cornell

(646) 962-2382 • kas9280@med.cornell.edu

- Advanced endoscopy
- Esophageal disease
- Liver disease

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NewYork-Presbyterian Hospital
525 East 68th Street
New York, NY 10065
www.nyp.org

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Redefining Selection Policies for HCC Liver Transplantation (continued from page 2)

"Some people argue that we're doing too many transplants for patients with HCC versus other patients, but I argue that we're not doing enough," continues Dr. Halazun. "We can give them an excellent, long-term survival, and they can do very well compared to many other diseases where we do transplant. The evolution will happen because the number of patients with hepatocellular carcinoma is rising. We have to figure out how we can give these patients a chance for a cure. Right now we're doing operations for patients with other cancers where the survival at five years is under 25 percent. While those are not liver transplants, even with those potentially bad results we still offer surgery to patients with the slim chance of cure. So, why not offer someone a transplant with a 70 percent chance of a cure?"

Reference Article
Halazun KJ, Tabrizian P, Najjar M, Florman S, Schwartz M, Michelassi F, Samstein B, Brown RS Jr, Emond JC, Busuttil RW, Agopian VG. Is it time to abandon the Milan criteria? Results of a bicoastal U.S. collaboration to redefine hepatocellular carcinoma liver transplantation selection policies. *Annals of Surgery*. 2018 Oct;268(4):690-99.

For More Information
Dr. Karim J. Halazun • kah7007@med.cornell.edu