In 2008 in Japan, Haruhiro Inoue, M.D., used a submucosal tunnel approach — a concept developed by Christopher J. Gostout, M.D., at Mayo Clinic in Rochester, Minnesota — to perform the first human endoscopic myotomy for achalasia. His technique, named peroral endoscopic myotomy (POEM), involved creating a mucosal incision (mucosotomy) after submucosal fluid injection; developing a submucosal tunnel along the esophagus that extends into the gastric cardia; meticulously dissecting the muscle layer (muscularis propria); and, finally, closing the mucosotomy site with clips.

Today, this endoscopic procedure is a universally accepted alternative to surgical myotomy. It has consistently achieved excellent outcomes, and has opened the door to minimally invasive treatment of other esophageal motility disorders.

Peroral endoscopic tumor resection (POET) is one of the offshoots of POEM and the first endoscopic technique capable of resecting tumors originating from the submucosa and muscularis propria. Dr. Inoue and colleagues first described it in 2012, and since then, POET has been used to successfully resect selected subepithelial tumors of the stomach and esophagus. Like POEM, POET is a safer and far less invasive alternative to surgical interventions such as partial gastrectomy or esophagectomy.

**Technique and indications**

POET starts with a submucosal fluid lift and mucosal incision approximately 5 centimeters proximal to the lesion. The submucosal tunnel is developed along the esophagus extending into the gastric cardia. The muscle layer is meticulously dissected and closed with clips. The subepithelial tumor is resected en bloc.

**Figure.**

A. Subepithelial mass in the middle of the esophagus. B. Mucosal incision (mucosotomy) 5 cm proximal to the lesion. C. Submucosal dissection and tunneling to the mass. D. Dissection of the mass within the submucosal tunnel. E. Post-resection defect and disrupted muscularis propria layer within the tunnel. F. Mucosotomy site. G. Closure of the mucosotomy site with endoscopic clips. H. En bloc resected specimen (leiomyoma).
proximal to the target lesion, followed by the creation of a submucosal tunnel to the level of the lesion using the same techniques described for POEM. While preserving the integrity of the mucosal layer and therefore preventing perforation, the subepithelial tumor is dissected free from its attachments using one or a combination of electrosurgical knives. The tumor is then removed through the mucosal entry, which is closed with endoscopic clips (Figure).

POET requires greater technical dexterity and may be more challenging than POEM, even for endoscopists who are proficient in it, according to Louis M. Wong Kee Song, M.D., a gastroenterologist who performs the procedure at Mayo Clinic’s campus in Rochester, Minnesota. “POEM is simple myotomy, whereas POET requires meticulous dissection of the tumor away from the mucosa and muscularis propria in a relatively confined space,” he says. “It requires an operator who is highly experienced with advanced resection and dissection techniques, and for that reason, POET will likely be limited to specialized centers with physicians interested in these procedures. It is definitely a niche practice.”

In the absence of suspected or proven malignancy of subepithelial tumors by tissue sampling or imaging studies, POET is indicated for gastrointestinal stromal tumors and leiomyomas in the esophagus, esophagogastric junction or gastric cardia that range in size from 2 to 5 cm. Although resection of lesions larger than 5 cm may be technically feasible, it is associated with a higher risk of complications; retrieval of large lesions through the mucosal incision site and esophagus also poses a challenge. Subepithelial lesions less than 2 cm are considered low risk and are usually managed with lifelong surveillance, although removing them potentially eliminates the need for monitoring.

POET may be considered for older patients or those with certain comorbidities, including obesity, who aren’t suitable candidates for surgery, according to Norio Fukami, M.D., who specializes in the endoscopic management of gastrointestinal cancers at Mayo Clinic’s campus in Arizona. He says conditions that preclude POET include severe cardiopulmonary disease and prior radiation therapy or endoscopic mucosal resection or ablation with resulting tissue fibrosis. Patients who have suspected or confirmed malignancy are referred for surgical resection.

Benefits
POET does not preclude salvage surgery and has been shown to result in reduced hospital time, lower costs and a significantly shorter recovery period. Similar to POEM, post-procedure observation in the hospital averages one day.

Dr. Wong Kee Song explains: “The day after the procedure, patients typically undergo a contrast media swallow study to check for mucosal integrity and leakage. If recovery is uncomplicated, they start a liquid diet on day one post-op and after about a week, they return to eating normally. Because this is such a new procedure, the optimal follow-up is still to be determined, but follow-up testing may not be necessary if complete curative resection is achieved.”

Although POET has been used successfully, long-term, multicenter studies of the technique’s efficacy and safety are needed. Such studies are difficult to coordinate and conduct because lesions targeted by POET are uncommon. Dr. Wong Kee Song’s group treats just five to 10 such lesions each year.

Still, he says, “If we are able to remove the tumor en bloc with negative margins, we feel confident that we have achieved a curative procedure.”

Hepatobiliary Neoplasia Clinics Noted for Superior Outcomes

Hepatocellular carcinoma (HCC) is the most common primary liver cancer in the United States and the leading cause of death in patients with cirrhosis. Although hepatitis C infection now accounts for 50 percent of cases, the growing burden of obesity, diabetes and nonalcoholic fatty liver disease — all independent risk factors for HCC — will likely drive further increases in chronic liver disease and liver cancer.

Many patients, however, not only lack access to novel cancer therapies but also to coordinated, guideline-based care. A survey of primary care physicians published in *Clinical Gastroenterology and Hepatology* in 2015 found that only half of physicians who saw patients with cirrhosis screened for HCC, and many were unable to identify effective cancer therapies.

Lewis R. Roberts, M.B., Ch.B., Ph.D., a researcher and clinician specializing in hepatic and biliary cancers at Mayo Clinic’s campus in Minnesota, says another barrier to quality care is a fragmented health care system in which
patients often wait months for a diagnosis. “By the time patients come to us, they are quite frustrated because their first imaging study was two or three months ago, and it took that long to get to the point where they are starting to be evaluated,” he says. “Here, we can accomplish the evaluation in a week or so by having all the necessary systems and procedures in place.”

Mayo Clinic’s liver cancer clinic in Phoenix, Arizona, also accommodates patients quickly, according to Thomas J. Byrne, M.D., a hepatologist specializing in liver disease and transplantation.

He explains: “Typically, patients rotate from radiology studies, consultations with hepatologists, subsequent consultations with surgeons or interventional radiologists as well as medical oncologists. It’s as if patients have to travel around the perimeter of a large wheel, visiting each spoke in a process that plays out over a fairly lengthy period of time. Our goal is to place the patient at the center of the wheel and have each of the individual specialties involved in care converge in the center on a single day of clinic.”

The same efficient, multidisciplinary approach extends to evaluation of indeterminate hepatic lesions, selected neuroendocrine malignancies that have spread to the liver and cholangiocarcinoma, which can present a particular diagnostic challenge, especially in the setting of primary sclerosing cholangitis.

“Our radiologists are highly experienced in imaging liver and biliary tract tumors and are often able to achieve a diagnosis without the need for biopsy,” Dr. Roberts says. “When biliary stenosis remains indeterminate after MRI or CT, we may recommend endoscopic retrograde cholangiopancreatography or endoscopic ultrasound followed by fluorescence in situ hybridization, which has been shown to improve tumor detection compared with conventional cytology.”

**Locoregional treatments**

Surgery is the preferred treatment for most resectable primary liver tumors and, increasingly, for a small number of colorectal liver metastases (CLM). At Mayo Clinic’s campus in Minnesota, about 15 to 20 percent of patients with CLM are eligible for potentially curative surgical resection, including those with multiple bilobar lesions and extrahepatic disease. In such cases, tumors may first be downsized with radiation or chemotherapy. Patients who are not candidates for resection because of tumor size, location or multifocality, or inadequate liver reserve, are reviewed at a multidisciplinary liver imaging review conference in which a variety of specialists generate a care plan that can usually be executed within one or two weeks, Dr. Byrne says. These patients may be offered locoregional therapies, including radiofrequency ablation, which, depending on tumor size and location, may have near-equivalence to surgery, transarterial chemoembolization and transarterial radioembolization.

**Liver transplantation**

As a three-site institution, Mayo Clinic has the highest volume of liver transplants in the nation with consistently excellent graft and patient survival outcomes. Waitlist outcomes also are excellent. In 2015, the number of waitlist transplants at Mayo Clinic hospitals in Florida and Arizona was statistically higher than expected, and waitlist mortality was half the national average, according to Scientific Registry of Transplant Recipients data.

“We have a demonstrably unique ability to take care of patients before, during and after transplant, including those with cholangiocarcinoma,” says Denise M. Harnois, D.O., a specialist in liver disease, hepatobiliary cancer and liver transplantation at Mayo Clinic’s campus in Jacksonville, Florida. “Mayo Clinic’s campus in Florida has one of the largest transplant programs in the world, and 20 to 30 percent of our patients are transplanted with a hepatobiliary malignancy. With adherence to a protocol of neoadjuvant chemoradiation originally developed at Mayo Clinic, these patients currently have a 70 percent survival rate of one to three years. Our outcomes are among the best in the southeastern United States as well as nationally.”

“The three Mayo transplant programs work together very closely in clinical care, research and education,” Dr. Roberts says. “There is a great synergy that happens when transplant groups get together on a regular basis and share best practices.”

**For more information**

Is Pentoxifylline the Drug for Treating Acute Pancreatitis?

Acute pancreatitis (AP) is an inflammatory condition of the pancreas characterized by upper abdominal pain, elevated blood levels of pancreatic enzymes and inflammatory changes on pancreatic imaging. Although there are many causes, chronic alcohol use and gallstones account for nearly 60 to 65 percent of cases in adults.

Most people — around 80 percent — have a mild form of AP that usually resolves within three to four days with supportive care. Others develop moderately severe disease characterized by organ failure lasting less than 48 hours, local complications such as acute peripancreatic fluid collections, pancreatic pseudocyst, acute necrotic collections and walled-off necrosis, or exacerbation of pre-existing comorbid conditions. Still others have severe disease with persistent organ failure.

Local complications, persistent organ failure and infectious complications are leading causes of morbidity and mortality in patients with severe disease. Thus, early identification of those most likely to develop moderately severe or severe AP is crucial for better outcomes. Most laboratory tests and severity scoring systems have limited predictive value, however, and the search continues for an ideal predictor or predicting system.

Guidelines from the American College of Gastroenterology, American Pancreatic Association and International Association of Pancreatologists suggest using risk factors such as advanced age, comorbidities, obesity, pleural effusion or pulmonary infiltrates, certain laboratory findings, and both persistent systemic inflammatory response syndrome and persistent organ failure as predictors of severe disease.

Yet even if high-risk patients are identified, no drugs exist to treat them. Treatment for severe AP involves monitoring with aggressive hydration and other supportive measures. In patients with established infected pancreatic necrosis or other complications, antibiotics or minimally invasive surgical interventions may be needed.

The potential of pentoxifylline

There are several reasons for the lack of pharmacological therapies for AP, according to Santhi Swaroop Vege, M.D., a gastroenterologist at Mayo Clinic’s campus in Rochester, Minnesota, and a leading expert on AP.

“Various drugs that seemed promising in animal experiments or small studies have not panned out in clinical trials,” he says. “Furthermore, it’s difficult to get enough patients in a single institution to conduct clinical trials for AP, and multicenter trials are fraught with logistical issues. Previous multicenter trials for AP in the U.S. have not been completed for logistical reasons.”

Mayo Clinic, however, admits about 300 patients with AP annually — enough to conduct a single-center trial. In the August 2015 issue of *Gastroenterology*, Dr. Vege and colleagues published the results of a pilot study of the nonselective phosphodiesterase inhibitor pentoxifylline in 28 patients with predicted severe AP. Participants were randomized to receive pentoxifylline or placebo within 72 hours of diagnosis. Those treated with the drug were admitted less often to the intensive care unit and had fewer hospital stays longer than four days compared with those treated with placebo — zero versus four days and two versus eight days, respectively.

Based on these results, Dr. Vege initiated a larger, NIH-funded, randomized, double-blind, placebo-controlled study whose aim is to determine whether inhibition of the tumor necrosis factor-alpha (TNF-a) pathway with pentoxifylline reduces inflammatory markers and improves clinical outcomes in AP. The study also looks at the drug’s safety and at patient tolerance. The trial is designed for all patients with AP who will be randomized within 72 hours of diagnosis to receive either the drug or placebo for three days or until discharge.

“Pentoxifylline seems particularly promising because it has two mechanisms of action. It blocks TNF-a, which has been shown in animal studies to reduce inflammation in AP, and it increases microcirculation in the small capillaries. The latter is important because microcirculatory occlusion in the pancreas, kidneys, lungs and other areas is an important pathogenic event in AP,” Dr. Vege explains. “Furthermore, pentoxifylline has a reasonable safety profile over many decades of use, is inexpensive and is taken orally. Many other AP drugs currently in the pipeline are costly, administered parenterally and lack safety data.”

He points out that although nearly 75 percent of patients with AP recover spontaneously in three or four days, distinguishing the 25 percent who won’t remains challenging.

“The methods for determining who will fall into that 25 percent are really not much better than the flip of a coin,” he says. “In the absence of a precise predictive model, we would like to find a simple, inexpensive drug with no side effects that can be given to all patients within the first 24 to 48 hours. Such a drug wouldn’t harm the 75 percent of patients with mild AP.
but would help prevent complications in those with predicted severe disease.”

He says pentoxifylline meets those criteria. The results of the current trial, which is enrolling all eligible patients admitted at Mayo Clinic’s campus in Minnesota, will likely be available by the end of next year. “No matter what the outcome, this will be a landmark study,” Dr. Vege says. “Even if it is negative, we will show that single-center trials are feasible for future AP clinical research.”

For more information


Radiologic Response Is Promising Treatment Target in Crohn’s Disease

Early, optimized treatment to meet specific therapeutic targets has significantly improved outcomes in cardiovascular disease, type 2 diabetes and rheumatoid arthritis. But treat-to-target strategies have only recently been adopted for inflammatory bowel disease (IBD), where treatment has traditionally focused on controlling symptoms.

The lack of correlation between clinical symptoms and disease activity is now well-established, however, and bowel inflammation and damage often continue in patients who are in clinical remission. Thus, treatment targets in IBD are changing to include not only clinical remission but also either mucosal healing or, in patients with Crohn’s disease (CD), deep remission — defined as mucosal healing plus steroid-free clinical remission. It is thought that these targets may alter the natural history of IBD by delaying or preventing disease progression.

It remains to be seen whether treating to target can change the disease trajectory. But early top-down therapy, in which a biologic anti-tumor necrosis factor (anti-TNF) agent such as infliximab or adalimumab is used as one of the first line treatments, has already been shown to improve disease-related outcomes, according to Edward V. Loftus Jr., M.D., a gastroenterologist and IBD specialist at Mayo Clinic’s campus in Rochester, Minnesota.

He points to the REACT trial, which involved 60 European and Canadian medical centers that see patients with Crohn’s disease. In all, nearly 2,000 patients were randomly assigned to usual management (a step-up model in which medical therapy was escalated in response to patient symptoms) or an algorithmic approach where patients were assessed for symptomatic, active Crohn’s disease every 12 weeks, with therapy advanced in those not in clinical remission. The results, published in The Lancet in 2015, found that although remission rates were similar in the two groups, patients following the clinical treat-to-target approach had fewer hospital admissions, surgeries and serious disease-related complications.

Radiologic response to therapy
Mucosal healing is generally assessed by ileocolonoscopy. But Michael F. Picco, M.D., a gastroenterologist specializing in IBD at Mayo Clinic’s campus in Jacksonville, Florida, says endoscopy may not be useful in small bowel CD because it can lack the ability to access the small bowel or assess penetrating intramural disease or proximal disease that skips the distal ileum.

Computerized tomography enterography (CTE) and magnetic resonance enterography (MRE) overcome many of these limitations. Both modalities are highly specific and sensitive for detecting active small bowel inflammation and have already been shown to identify transmural radiologic response with medical therapy.

In a study published in The American Journal of Gastroenterology in 2016, David H. Bruining, M.D., and Parakkal Deepak, M.B.B.S., and colleagues described a retrospective cohort of 150 patients with established small bowel CD who underwent serial CTE or MRE imaging or both at Mayo Clinic’s Minnesota campus between 2002 and 2014. About half the patients (49 percent) had ileal disease, 45 percent had a nonstricturing, nonpenetrating phenotype and 28 percent had a history of perianal disease.

Based on the second imaging assessment, 55 patients (37 percent) were classified as complete Radiologic Response Is Promising Treatment Target in Crohn’s Disease
responders, 39 (26 percent) as partial responders and 56 (37 percent) as nonresponders. Complete or partial responders had fewer hospitalizations and less need for rescue corticosteroids compared with nonresponders; complete responders also had fewer CD-related surgeries (Figure).

This was the first study to demonstrate that treating to a transmural target identified on CTE or MRE is feasible and may, in fact, be the only target for patients with disease inaccessible to standard endoscopy due to fibrostenotic narrowing of the small intestine.

“We are moving away from the reactive, symptom-driven approach to IBD therapy,” Dr. Loftus says. “In patients deemed at high risk of intestinal complications, we now go immediately to an aggressive, top-down approach. That includes patients diagnosed at a younger age, those with ileal, ileocolonic or proximal GI involvement, and those who present at baseline with fistula or abscess. In addition to our study, we are starting to see data from other centers confirming that this approach leads to fewer disease-related complications, better mucosal healing, and reduced rates of surgery and hospitalization. These benefits must be kept in mind that many patients will achieve and maintain remission on traditional step-up care."

Dr. Picco says his group practices the treat-to-target approach to demonstrate significant objective response to therapy, if not mucosal healing, among patients with clinical improvement.

“For patients with response or remission, we are proactive in assessment with both ileocolonoscopy and enterography before clinical recurrence develops. The study by Dr. Deepak and colleagues suggests that radiographic response is an important treatment target to predict recurrent disease and guide therapy, and it supports our current practice of proactive follow-up,” he says.

For more information

Individualized Medicine as a New Paradigm for Obesity Management

Nearly 70 percent of adults in the United States are obese or overweight. Obesity negatively affects almost every organ system in the body and increases the risk of associated comorbidities such as type 2 diabetes, hypertension, cardiovascular disease and cancer. Yet despite increased understanding of the pathophysiology of obesity, outcomes of current weight-loss strategies, including diet and exercise, medications, and surgery, are highly variable.

For example, extended-release (ER) phentermine-topiramate, a recently approved obesity medication, is associated with an average 9.8 percent weight loss, and 30 percent of patients lose less than 5 percent of their body weight. Bariatric surgery has a better track record, with Roux-en-Y gastric bypass resulting in a more than 60 percent reduction in excess weight as well as resolution of diabetes and other comorbidities. But only about 1 percent of patients who qualify for the surgery undergo it, and of those who do, around one-third eventually regain a significant amount of weight.

According to Andres J. Acosta Cardenas, M.D., Ph.D., an obesity specialist at Mayo Clinic’s campus in Rochester, Minnesota, the varying efficacy and outcomes of obesity treatments are due, in part, to gastrointestinal and psychological traits that are unique to each individual. “Obesity is a heterogeneous disease, and people gain weight for many different reasons. We cannot expect to have a one-size-fits-all solution,” he says.

Dr. Acosta and colleagues studied specific traits associated with a high body mass index (BMI) in a trial that aimed to identify phenotypes and latent dimensions in obesity and to validate the use of quantitative traits to predict short-term weight loss in response to pharma-cotherapy and bariatric endoscopy.

The study, which was published in Gastroenterology in 2015, involved 509 normal-weight, overweight and obese adults who were tested for gastrointestinal function, satiation and satiety. The results showed that people who are obese have significant differences in gastrointestinal quantitative traits compared with those of normal weight, including lower satiation, accelerated gastric emptying, increased fasting gastric volume and decreased peak postprandial serum peptide YY.

The researchers subsequently validated the applicability of obesity-related gastrointestinal quantitative traits in two randomized clinical trials. The first was a double-blind placebo-controlled study that examined the effects of ER phentermine-topiramate on gastric functions, satiation, satiety and relevant gut hormones as well as predictors of response to treatment. Results demonstrated that abnormal satiety at baseline predicted weight loss with ER phentermine-topiramate.

Another placebo-controlled trial studied the effect of the incretin mimetic exenatide on gastric emptying, satiety, satiation and weight loss in 20 obese patients with accelerated gastric emptying. That trial, published in 2015 in Physiological Reports, found that the drug had a significant effect on gastric emptying of solids and also reduced calorie intake at a buffet meal by an average of 130 kilocalories compared with placebo. An earlier accelerated gastric emptying test predicted weight loss with exenatide.

Translation into clinical practice

Dr. Acosta says that based on better-than-expected results in these trials, Mayo Clinic will begin using an individualized approach to obesity management in which the predominant phenotype of each patient will be matched with the most appropriate and effective weight-loss therapies based on mechanism of action. This novel approach involves a multidisciplinary team of obesity medicine and nutrition physicians, nurses, psychologists, dietitians, physical therapists, bariatric endoscopists and surgeons. He also says this state-of-the-art individualized approach, which focuses on the right intervention for the right patient, is long overdue.

“In a clinical setting, what do you tell patients when you have five approved weight-loss medications, three approved devices and four different surgeries and know that only about one-third will respond to these interventions? We need to be able to identify the right tools to combine with lifestyle changes to maximize weight loss and minimize complications. Patients are frustrated with the current treatments because most of them fail — and that’s because we’re not addressing the underlying problem. Identifying the problem and prescribing the right medication, device or surgery to treat it will provide superior results,” Dr. Acosta explains.
For more information


In the News
Mayo Clinic Distinguished for Pancreatic Cancer Care
Mayo Clinic’s campus in Rochester, Minnesota, has been designated a Pancreatic Cancer Center by the nonprofit National Pancreas Foundation. These centers are considered premier health care facilities for the multidisciplinary treatment of pancreatic cancer, with a focus on the best possible outcomes and improved quality of life.

Education Opportunities
For more information or to register for courses, visit www.Mayo.edu/cme/gastroenterology, call 800-323-2688 (toll-free) or email cme@mayo.edu.

Mayo Clinic Gastroenterology and Hepatology 2017
March 16-19, 2017, in Orlando, Fla.

2nd Annual Gastrointestinal Advances in Endoscopy and Minimally Invasive Surgery: Where Are We in 2017?

Real World Inflammatory Bowel Disease, Dilemmas and Discussion 2017
Oct. 7, 2017, in Minneapolis