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The Minimally Invasive Revolution in GI Endoscopy: An Interview with Kenneth Chang

Kenneth Chang, MD, a thought-leader in the field of gastrointestinal endoscopy, speaks about the migration of surgery to less invasive procedures that is changing gastroenterology as it has so many other clinical specialties. Innovations here promise to increase the numbers of patients who get treated for some difficult conditions.

by
MARY STUART

Gastrointestinal endoscopy is picking up speed in a field where there are surgical predicates for several diseases that are not only uncomfortable for patients but are, in many cases, associated with pathological changes that predispose patients to cancer. These include gastroesophageal reflux (GERD), obesity, achalasia, esophageal diverticula, Barrett's esophagus, esophageal and stomach cancer, and gastric outlet obstruction.

These non-surgical procedures promise to help many sick patients who miss the eligibility cut-off for surgery—patients who are obese for example, but who, with a body mass index of 30 fall under the threshold for bariatric surgery, or the 30-35% of patients with GERD whose disease has already caused anatomic alterations that are the beginning of a downward spiral, but who are not deemed to have disease severe enough for surgery. They also promise to address the large numbers of patients who choose not to have surgery because of the risks of going under the knife, side effects, or known rates of complications. Here, as in cardiology and many other specialties that have gone the less invasive route, minimally invasive interventions might come with fewer post-procedure side effects, lower treatment costs and other post-treatment economic benefits.

There is now a body of long-term data demonstrating durability out to five or even ten years for some interventional gastrointestinal treatments. In GERD, for example, **Restech** (**Respiratory Technologies Corp.**), which markets the *Stretta* radiofrequency device, which thickens the lower esophageal muscle, and **EndoGastric Solutions Inc.**, developer of the *TIF 2.0* (Transoral Incisionless Fundoplication) procedure, which, among other approaches, adheres most closely to the predicate surgical Nissen fundoplication procedure, both have long-term data (*see "EndoGastric Solutions Ushers in a New Day for GERD Interventions," this issue*). **Johnson & Johnson**'s *LINX* (developed by Torax Medical) a ring-shaped implant containing magnets, which augments the esophageal sphincter, is also on the market in the US.

Many gastroenterological conditions go hand in hand—obesity and GERD; GERD and Barrett's esophagus; and Barrett's esophagus and esophageal cancer—and warrant treating sooner rather than later because of the mutually destructive effects of such co-morbidities, and, as noted, a heightened risk of cancer.

Endoscopic procedures can help here, and the specialty is changing to accommodate them. It's getting to the point where numerous co-morbid conditions can be treated endoscopically so patients can avoid invasive surgery altogether. At the same time, the specialty is increasingly embracing both surgery and endoscopy in multi-disciplinary practices, a trend solidified by the recent formation of the American Foregut Society, the stated goal of which is "to help guide both the diagnosis and management of foregut

disease through collaboration between gastroenterologists and foregut surgeons."

Strategics are taking notice of the space; **Boston Scientific Corp.**, **Medtronic plc**, Johnson & Johnson, and others have been placing bets by acquiring interventional GI start-ups (*see Figure 1*). To learn more about what medical device companies should be watching out for in this space, *MedTech Strategist* spoke with Kenneth Chang, MD, a thought-leader in endoscopic-based interventional procedures treating a variety of foregut conditions.

Chang is a founding board member of the newly-formed American Foregut Society, and executive director of the multidisciplinary GI practice, the H.H. Chao Comprehensive Digestive Disease Center, which is part of the University of California Irvine's School of Medicine. Chang is internationally recognized for developing, over a 25-plus year career, advanced expertise in gastrointestinal endoscopy and technologies that advance the field, including the first endoscopic ultrasound-guided fine needle aspiration system, and novel technologies for endoscopic ultrasound-guided fine needle injection. His active areas of research and development include the *in vivo* identification and diagnosis of pancreatic cystic neoplasms with needle-based pressure gradient measurement, and indeed, most recently, he notes that he has been focused on the endoscopic treatment of conditions associated with the development of cancer.

[Editor's note: *Potential conflict-of-interest disclosures for Dr. Chang include relationships with Apollo Endosurgery, Boston Scientific, Erbe, C2 Therapeutics, Cook Medical, Medtronic/Covidien, EndoGastric Solutions, Mederi Therapeutics, Olympus, Ovesco, Pentax, and Torax.*]

Figure 1

Selected Recent Acquisitions in Minimally Invasive Gastroenterology

Companies	Technologies Acquired
(3/2018) Boston Scientific acquired EMcision	Developer of an endoscopic bipolar RF device that coagulates tissue inside the GI tract to treat pancreaticobiliary cancers
(12/2017) Medtronic acquired Crospon for $45 million	Gains *EndoFlip*, a functional luminal imaging probe that creates a picture of the geometry of the esophagus, pylorus and anal sphincters; and *EsoFlip*, which enables clinicians to measure stricture size
(03/2017) Johnson & Johnson acquired Torax	Implanted in a laparoscopic procedure, Torax's *LINX* implant for GERD consists of interlocked titanium beads with magnetic cores, for augmenting the esophageal sphincter
(01/2017) Pentax Medical (HOYA Group) acquired C2 Therapeutics	Developer of the *C2 CryoBalloon Ablation System*, which uses extreme cold to ablate precancerous Barrett's esophagus endoscopically

Source: Company websites

MedTech Strategist: ***I found it interesting, in your recent paper in the World Journal of Gastroenterology, that you describe interventional treatments for the GI tract in terms of preventing cancer. Could you elaborate on that for us? [Kenneth J Chang, "Endoscopic foregut surgery and interventions: The future is now. The state-of-the-art and my personal journey," World Journal of Gastroenterology,* January 7, 2019.]**

Kenneth Chang: I have an endowed chair in this topic, "GI Endoscopic Oncology." It focuses on how endoscopy can help with cancer management, from early detection to diagnosis, to staging, to treatment to intervention.

Less invasive interventions are often based on surgical predicates. Is that the case in gastrointestinal endoscopy?

Yes, that is most definitively the trend, and that's why our brand new society, the American Foregut Society, which just had its inaugural meeting in Vegas a few months ago, was formed. The traditional foregut surgeons realized that if they stay siloed and don't get into the endoscopy space they'll become dinosaurs. There is a real effort to bring endoscopic intraluminal strategies into this field and to take down the walls; to make it more fluid so specialists can move towards the less invasive treatment options.

In some cases, as open surgeries move to minimally invasive procedures, some degree of efficacy is exchanged for a lower degree of invasiveness. How does this transition play out in gastroenterology?

Let's take the GERD space. Huge problem. There is a therapeutic gap between PPIs [drugs known as proton

pump inhibitors], as good as they are, and the anatomic plumbing problem we are dealing with. PPIs address the pH and the acidity, but they don't really address the reflux and the regurgitation.

On the other side, we have the traditional laparoscopic Nissen fundoplication, which is very effective with durability of 8-10 years. Side effects are considerable—gas bloat and flatulence; patients can't vomit or belch—so people decide they're not so unsatisfied with their medical treatment because they aren't willing to make the leap to have this operation.

On the surgical side, there have been iterations in improvement from the full laparoscopic Nissen fundoplication to the partial Nissen fundoplication, to the *LINX* procedure [the non-surgical *LINX Reflux Management System*, which uses an implant to shore up the lower esophageal sphincter] which has decreased some of those side effects, but not enough.

The endoscopic approach, where we can now do an endoscopic fundoplication, hits a real need and it fills some of that therapeutic gap. That's the *EsophyX* device from EndoGastric Solutions. Their transoral incisionless fundoplication [*TIF 2.0*] has been shown in prospective clinical trials to be very effective.

Do these different approaches deal with the same problem, or are they specific to particular types of disease?

It is important to apply them according to where the patient is, on a personalized level, with respect to where the anatomy distortion is. There is a spectrum from minimal to no anatomic alteration; from mild to moderate to severe. The further to the right the patient is on the spectrum, the more surgery is necessary because there are three parts to anti-reflux surgery; reducing the hernia, tightening the diaphragm and creating the valve or the fundoplication.

Patients in the early part of the spectrum don't need hernia reduction, because there is no hernia. They don't need a diaphragmatic crural repair, because there is no open hiatus. They just need a strengthening of the weak valve, and the creation of a flap valve or high pressure zone, and that can now be done well and safely with an endoscopic procedure like the *TIF 2.0* procedure. In this scenario, the endoscopic approach does not replace the surgical approach, but it is positioned where surgery, in this patient profile, would be overkill.

Now we can more appropriately give the patient the least invasive procedure tailored to their individual need. Multiple approaches address the spectrum issue, where you don't have to use a grenade where a sniper rifle is sufficient.

Since GERD is a function of various alterations in different portions of the anatomy, does that influence therapeutic device development? It sounds like you are saying that rather than finding a one-size-fits-all device that can treat all patients, it is important to offer a range of things so you can offer the least invasive approach for whatever is causing the patient's symptoms.

Absolutely. There are other scenarios where endoscopy could be a replacement for surgery, for example, in patients with difficulty swallowing because of achalasia. Achalasia is a condition where the esophagus is weak and/or there is no peristalsis [ability to move a bolus of food to the stomach], and the lower esophageal sphincter does not open in response to swallowing. The traditional treatment has been a surgical one, which has gone from an open surgery, to the laparoscopic Heller Myotomy.

The myotomy cuts the muscle and releases the valve that doesn't want to open. The endoscopic equivalent is called the POEM procedure, which stands for Per-Oral Endoscopic Myotomy. In various studies and meta-analyses, the POEM procedure has been shown to actually be superior to the established surgical procedure, the Heller Myotomy, so in this case, the POEM may replace the Heller. In the GERD situation, it's a matter of treating the patients where they are on the spectrum, where one may replace the other as a less invasive alternative.

In some specialties like cardiovascular, you might use an interventional approach to keep the disease from getting worse. It's the same disease process, but you are intervening earlier in its course. Could the same be said for GERD, or not really, since is a function of anatomic alterations from different causes?

Well, it hasn't been proven—it would probably take 30-year studies—but there is a real sense that if you don't do anything for someone who is early on in the spectrum, they will continue to move along the spectrum. A small hernia starts sliding more, it dilates the diaphragm more, the hernia gets larger, and you progress further down the spectrum. Most experts in the field would agree with the notion—and again, this has not been proven—that if you intervene before the small hernia becomes larger, or when the loose valve has not yet herniated, you may be able to stop this ongoing cycle of deterioration.

Is there one approach today that addresses more of the contributors to GERD than another?

We can't say so, not yet, because we don't understand fully the pathophysiology and mechanisms of GERD. There has been quite a bit of work in this space, and there are some very interesting pieces of the puzzle. The diaphragm muscle is very important, and the few histologic studies that have looked at the integrity of the diaphragm muscle have shown that the diaphragm muscle is abnormal. So which came first—did the myofibrils [muscle fibers of the diaphragm] quit so the diaphragm became loose and that started the whole thing? And is it genetic, or did the hernia come first, and the hernia made the diaphragm muscles stretch? Or did the diaphragm muscle weaken and cause the hernia? The chicken and egg question is not well answered. So I don't think there is one device or therapy that can solve it. In coronary artery disease, if you could stop plaque formation, then you'd have it. We haven't found that yet in GERD.

Let's talk about how some of the new endoscopic therapies have made a difference in patients, starting with the* TIF 2.0 *procedure.

For a long time we thought, well, there are anatomic alterations and all we need to do is fix them and you'll be good to go forever. One laparoscopic Nissen fundoplication and we're done. We don't think that's the case anymore. GERD is a chronic condition. We can treat it, make it better, navigate around it and alleviate some of the symptoms, but it is a chronic condition.

With that in mind, *TIF 2.0* comes in and addresses a strongly felt need in patients who only partially respond to PPIs. They might say that their heartburn is not as bad when they're taking *Nexium*, but they still have regurgitation; when they bend over, everything comes up. They can't lie flat at night, and their cough keeps waking them up. In the past, those patients have been offered surgery as an alternative, but they've decided to live with their symptoms.

So *TIF 2.0* is solving a real unmet need. Here is a nonsurgical, minimally invasive procedure that can give me three to five years of good relief and keep me off these medications. We don't have level one data beyond five years yet but there are studies showing longer-term durability. But say it last for five years. Now a 35-minute noninvasive procedure gives my patients five years of relief from a chronic condition. I can get them off their PPIs and help improve their quality of life. And five years from now if things get loose, I can perform a simple *TIF 2.0* touch-up procedure, or they may need a surgery. But they have gained five years off of PPI therapy.

That is the impact for patients. It is giving them an alternative and reasonable durability of symptomatic control. And not only symptomatic control, but acid reflux can lead to Barrett's which can lead to cancers.

Are there any other GERD interventions that you work with?

There is an older procedure called *Stretta;* it has gone through three companies now, Curon Medical was the first, then Mederi Therapeutics and now it belongs to Restech. [Respiratory Technology Corp., which acquired *Stretta* from Mederi Therapeutics Inc. in 2018.]

That is a catheter-based procedure with a balloon that inflates at the valve and four needle electrodes go out into the muscle and deliver heat energy. The procedure takes about 20 minutes. I have been doing it for 15 years. It works best for patients who are in the very early part of the spectrum. They don't have a hernia, they don't have an open diaphragm, and their lower esophageal sphincter actually does work, it can close, but during the day when patients are up and about and eating and drinking diet coke, there is inappropriate relaxation of the sphincter. The *Stretta* device has demonstrated that for those patients it can decrease these inappropriate relaxations. However, in the past, I think the company or companies might not have understood the box that they played best in and might have overstated their claims, so this technology has suffered from a failure to meet expectations.

So, because of this disease spectrum that you describe, patient selection is key.

Exactly.

Many GI diseases go hand in hand—GERD, Achalasia, Barrett's esophagus, obesity. How does that influence your choice of therapy, or how should it influence therapy development? Is it important to always be able to preserve future treatment options?

It is becoming very clear to me that obesity and GERD are synergistically bad. Patients who are obese are more likely to have GERD; and obese patients are also less likely to respond well to GERD treatments and strategies. GERD and obesity both increase the risk of cancer. Obesity is

an epidemic in our country, and GERD is also increasing. Esophageal cancer is growing at an alarming rate. So these things tie in together and represent a huge population health problem for us.

We know that bariatric surgery works, not perfectly, but it works. Patients can lose 50 to 150 pounds and as a result, they reduce their risk of cancer, cardiovascular disease, diabetes, and overall mortality. If we could curtail obesity that would have a huge impact on the health of our society.

Where endoscopy is very interesting and exciting is, again, in that space between diet, exercise and diet pills, and a gastric bypass or a gastric sleeve. You have people that, with a BMI of 30, are technically obese, but are out of luck. They haven't reached a BMI of 35, which is the criteria for any type of surgery. [In order to be eligible for bariatric surgery a patient needs a BMI of 40 or a BMI of 35 plus a co-morbid condition.] Patients with a BMI of 30-35 have bad reflux, knee problems, back problems, and as they enter their fifth decade of life their cancer risk is climbing. There is a real need in this space.

Could you combine endoscopic treatments for obesity and GERD?

Yes. We have done combination procedures, where I have gone in and done a *TIF 2*.0 followed by an endoscopic sleeve gastroplasty, trying to hit both of those risk factors.

What is the climate like for innovation in interventional gastroenterology?

There are different aspects to that question. The GI endoscopy device innovation space is very large with unlimited possibilities, and I think a lot of venture capital folks understand that and would gravitate to devices in the digestive disease space. But in the GERD space specifically, there is a bit of post-traumatic stress. There is a graveyard of devices that have come and gone over 30 years—*Plicator* [**NDO Surgical Inc.**], *Enteryx* [Boston Scientific], other suturing devices—so investors are a bit leery of investing in another GERD device.

What would you say to those investors?

Two devices are now FDA approved with CPT codes and reimbursement. Companies like EGS, which have invested heavily in gaining long term level 1 and level 2 clinical evidence, should make investors more confident to invest in a space where there is a significant unmet need. We have broken the sound barrier! The Trojan horse is in the city.

But we are just beginning to understand GERD mechanisms so there are a lot of opportunities to understand them better and to tailor our device approaches towards those mechanisms.

What should we be looking to for the future?

In terms of what I think is coming up next? Combining things. For example, although POEM seems to be better than the Heller myotomy for relief of dysphagia, there is more GERD after the POEM procedure. Now, for the 10% or fewer of patients who have GERD after the POEM procedure, we have *TIF 2.0* to fix that. Now we can fix an endoscopic problem with an endoscopic solution without having to send the patient to surgery, which would beg the question of why we didn't send them to surgery in the first place! All of a sudden, two endoscopic approaches combine to create a complete strategy.

Look at Barrett's esophagus. Fifteen years ago, the standard of practice for someone with Barrett's esophagus with high grade dysplasia was esophagectomy—taking out the esophagus. That would be unheard of now. We are ablating, freezing, resecting the mucosa, and now Barrett's can essentially be treated and cured by endoscopy. Now we have a bunch of patients who used to have Barrett's but they still have GERD and want to get off their PPIs so we treat them with *TIF 2.0*. Again, one endoscopic solution dovetails with another endoscopic solution.

What are some other unmet clinical needs that might represent large markets for companies developing endoscopic solutions?

Millions of Americans—about 30% of the adult population—have acid reflux, but we have no idea who to screen, and how to screen a population for precancerous Barrett's. If there was a stool test, a blood test, a *Cytosponge* [Medtronic's minimally invasive device for collecting cells from the surface of the esophagus, which gained FDA approval in February 2019] for screening a population, that would be your next colon polyp/colon cancer story. Everyone gets screened for Barrett's, you go in and treat it the same way a polyp gets removed in the colon, and we wipe out that kind of cancer.

Unfortunately, that is a huge unmet need. We don't know how to screen well, so we are only intervening and making a

difference in a relatively small number of patients and barely making a dent in the epidemiology of esophageal cancer.

Are there some untapped areas that companies should think about?

Liver disease is another interesting area. We are working on devices to get us into the liver to take high-quality liver biopsies minimally invasively. There is a lot of non-invasive imaging technology for the liver. For example, I'm working with one company to develop a simple, needle pressure-measuring system that can measure the pressure inside the two main blood vessels that bring blood to and from the liver. That pressure difference or gradient is a key predictor of liver disease, prognosis, and overall health of the liver.

Endo-Hepatology is an exciting area. We can build bridges from one lumen of the gut to another and essentially do a bypass with ultrasound, needles, and stents, so that you never have to open the abdomen. We are now doing gastrojejunal anastomosis with endoscopy. [Chang, "Endo-Hepatology: A New Paradigm," *Gastrointestinal Endoscopy Clinics of North America,* April 22, 2012.]

What's your final word to innovators in this space—what should they be working on, what do you think they don't know

No one likes to hear this, but, be patient! A lot of these things take years to get through the various regulatory phases until you are in the marketplace. If investors aren't patient, they will cut short important innovation.

What would they like to hear?

The digestive disease space for devices is hot because we are definitely trending from open, to laparoscopic, to robotic to endoscopic. That movement is just getting started and everyone understands that trend. The formation of the American Foregut Society tells us that this is the trend. Industry needs to partner right along because there are plenty of innovative opportunities.