



Endoscopic closure devices (with videos)

Prepared by: ASGE Technology Committee

Mark Hanscom, MD,¹ Jorge V. Obando, MD,² Kumar Krishnan, MD,³ Amit Bhatt, MD,⁴ Juan Carlos Bucobo, MD,⁵ Andrew P. Copland, MD,⁶ Vinay Chandrasekhara, MD,⁷ Samuel Han, MD, MS,⁷ Allon Kahn, MD,⁸ Nikhil A. Kumta, MD, MS,⁹ Mansour A. Parsi, MD, MPH, MBA,¹⁰ Monica Saumoy, MD, MS,¹¹ Guru Trikudanathan, MD,¹² Arvind J. Trindade, MD,¹³ Julie Yang, MD,¹⁴ David R. Lichtenstein, MD,¹⁵ Ryan J. Law, DO,⁷ ASGE Technology Committee Chair

New York, Brooklyn, New York; Raleigh, North Carolina; Boston, Massachusetts; Cleveland, Ohio; Charlottesville, Virginia; Rochester, Minnesota; Scottsdale, Arizona; Memphis, Tennessee; Plainsboro, New Brunswick, New Jersey, USA

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(footnotes appear on last page of article)

The American Society for Gastrointestinal Endoscopy (ASGE) Technology Committee provides reviews of existing, new, or emerging endoscopic technologies that have an impact on the practice of gastrointestinal (GI) endoscopy. Evidence-based methods are used, with a MEDLINE literature search to identify pertinent clinical studies on the topic and a Manufacturer and User Facility Device Experience (U.S. Food and Drug Administration Center for Devices and Radiological Health) database search to identify the reported adverse events (AEs) of a given technology. Both are supplemented by accessing the “related articles” feature of PubMed and by scrutinizing pertinent references cited by the identified studies. Controlled clinical trials are emphasized, but in many cases data from randomized controlled trials are lacking. In such cases, large case series, preliminary clinical studies, and expert opinions are used. Technical data are gathered from traditional and web-based publications, proprietary publications, and informal communications with pertinent vendors. Technology status evaluation reports are drafted by 1 or 2 members of the American Society for Gastrointestinal Endoscopy Technology Committee, reviewed and edited by the committee as a whole, and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy. When financial guidance is indicated, the most recent coding data and list prices at the time of publication are provided. For this review, the MEDLINE database was searched through November 2023 for articles related to endoscopic closure of perforations, leaks, and fistulas by using additional relevant key words such as “intestinal fistula,” “perforation,” “over-the-scope clip,” “endoscopic clips,” “endoscopic suturing,” and “endoscopic closure,” among others. Technology status

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Endoscopic techniques have emerged as minimally invasive, nonsurgical therapeutic options to treat transmural defects of the gastrointestinal wall. Three distinct transmural defects of the GI tract can be broadly classified into perforations, leaks, and fistulas.¹ Perforations are acute, full-thickness injuries of the gut wall and may be spontaneous or iatrogenic. Leaks are typically postsurgical disruptions of the intestinal wall at the site of anastomosis leading to extravasation of GI contents from the intraluminal to extraluminal space through the defect. They are typically less acute in onset than perforations. Fistulas are chronic communications between 2 epithelial lined structures and, when arising from the GI tract, communicate with another portion of the bowel, skin, or other organ (eg, bladder, vagina). Chronic fistulas may occur after prolonged surgical leaks, inflammatory bowel disease, malignancies, infections (eg, tuberculosis, actinomycosis), and radiation therapy.

The incidence of iatrogenic endoscopic perforations ranges between 0.01% and 0.60% for diagnostic and 0.6% to 5.5% for therapeutic procedures.^{2,3} Spontaneous perforations of the luminal GI tract may be seen with ulcers, Boerhaave syndrome, and malignancy. Leaks are common AEs of bariatric surgery, with rates varying from 0.4% to 5.6% after Roux-en-Y gastric bypass and 1.9% to 5.3% after sleeve gastrectomy.⁴ Leaks often present with postoperative fluid collections, abscesses, or

persistent output from surgical drains. Fistulas are the most difficult transmural defect to close because of an established epithelial tract and poorly vascularized adjacent tissue. The epithelium of the inlet and tract lumen is often disrupted endoscopically with brushes or thermal therapy such as argon plasma coagulation prior to mechanical closure.

The optimal management of intestinal wall defects will be dependent on several factors including the etiology, acuity of injury, size of the defect, location, and clinical presentation. Multidisciplinary input from therapeutic endoscopy, surgery, and interventional radiology services is beneficial in determining the preferred approach. While endoscopic closure is now often considered for the initial treatment of GI defects, the foundational principles of surgical closure still apply. Healing of transmural defects throughout the GI tract begins with reapposition of the bowel wall and progresses through a sequence of hemostasis and inflammation, proliferation, maturation, and remodeling to re-establish tissue integrity.⁵ The strength of an anastomosis depends on both the formation of a water-tight seal on the serosal side and the suture-holding capacity of the intestinal wall, particularly the submucosal layer, which possesses the highest tensile strength.⁶ To optimize the resilience of an anastomosis, it should be tension free, well-perfused, adequately nourished, and free from infection. In regular wounds, maximum strength is reached after 6 weeks of healing.⁶ However, appropriate healing can be impacted by several factors, including poor nutrition, metabolic diseases, immunosuppression, infection, retained foreign bodies, and radiation, among others, which should be counteracted, when possible, to prevent poor healing and the development of chronic wounds.^{5,6} Perforations recognized during an endoscopic procedure are closed at the time of the initial procedure and in some circumstances (eg, postcolonoscopic mucosal resection [EMR] and endoscopic submucosal dissection [ESD] muscularis propria injury) closure is performed in a prophylactic manner to prevent delayed perforation. Many defects are repaired endoscopically using more than 1 technical closure technique or device, and selective sequential application is necessary depending on the initial clinical response to therapy.

TECHNOLOGY UNDER REVIEW

Endoscopic closure is often considered for the initial treatment of transmural defects throughout the GI tract, including perforations, leaks, and fistulas. The various endoscopic treatment modalities for endoscopic closure include endoscopic clipping (both through-the-scope [TTS] and over-the-scope [OTS] clips), over-the-scope suturing, through-the-scope suturing, and application of tissue sealants. Tissue sealants are often Food and Drug Administration (FDA)-approved medications used in an

off-label manner when applied for endoscopic closure of tissue defects, and include cyanoacrylate glue, fibrin sealant, and cardiac septal occluders. This review focuses on endoluminal therapies that close transmural defects within the GI tract. Previous ASGE technology documents have described the management of unique postoperative leaks and fistulas in the bariatric setting.⁷ This document also focuses on new closure technologies such as endoscopic suturing and newly modified TTS clips for closure of defects following EMR, ESD, and mucosal incision entry sites with third-space endoscopy, as the other methods for closure are discussed in previous ASGE technology documents.^{8,9} Standard nonendoscopic approaches to managing transmural luminal GI defects will not be discussed in detail as the focus of this technology document will be restricted to the closure techniques, their outcomes, and adverse events. For example, diagnostic strategies, decisions regarding timing of defect closure, role of peritoneal contamination in treatment decision, antibiotic administration, carbon dioxide (CO₂) insufflation, drainage of associated fluid collections, imaging studies, and hospitalization are discussed in other review and guideline documents.^{1,10-13} In this document, we will not cover other endoscopic management approaches for fistulas and perforations that do not involve closing a defect, such as diversion using a covered self-expandable metal stent (SEMS), endoscopic internal drainage, or endoscopic vacuum therapy. These alternatives may be effective in many patients with chronic leaks and fistulas but are beyond the scope of this report.

ENDOSCOPIC CLIPPING

Endoscopically placed clips (endoscopic clips) are widely available tools for hemostasis, site marking, and defect closure. There are 2 types of endoscopic clips: TTS and OTS. TTS clips are most commonly used, because they are easy to apply without the need for endoscope removal. Comparatively, OTS clips require a more advanced skill set while providing a more robust tissue approximation.¹⁴

THROUGH-THE-SCOPE CLIPS

The first use of TTS clips was reported for endoscopic hemostasis in Japan in 1975 and in the West in 1993.¹⁵⁻¹⁷ Endoscopic clips evolved to their current form by incremental improvements. The first TTS endoscopic clips available in the United States were manually reloadable with a clip applicator. In 2002, single-use, preloaded endoscopic clips were introduced. A control handle with precise clip rotation capability was added as a feature in 2016. Wider jaws for treatment of larger defects were introduced in 2018. Currently available clips offer the following common features: (1) single-use, (2) repeated

TABLE 1. Through-the-scope clips

Manufacturer	Length (cm)	Jaw size (mm)	Minimal channel size (mm)	Price (USD)/No. in box	Material	Special features
Boston Scientific						
Resolution	155/235	11	2.8	330	Stainless steel, cobalt chrome, styrene	
Resolution 360	155/235	11	2.8	370	Stainless steel, cobalt chrome, styrene	
Resolution Ultra	155/235	17	2.8	370	Stainless steel, cobalt chrome, styrene	
MANTIS	235	N/A	2.8	325	Stainless steel, cobalt chrome, styrene	Modified anchor prongs to minimize slippage of tissue
Cook Medical						
Instinct Plus	207	16	2.8	2700/10	Stainless steel, Delrin, nitinol	
Olympus Corp.						
QuickClip2	165	8	2.8	713/5; 2726/20	Stainless steel	
QuickClip Pro	165/230	11	2.8	3700/10	Elgiloy	
EZ Clip	165/230	7, 9.5, 11	2.8	1700/40	Stainless steel	Reloadable
ConMed						
DuraClip for Gastroscopy	165	11	2.8	3000/10	Stainless steel	Short postdeployed stem
DuraClip for Colonoscopy	235	11, 16	2.8	3000/10	Stainless steel	Short postdeployed stem
Diversatek						
RePlay	230	11, 16, 18	2.8	2000/5	Stainless steel	
Manufacturer	Length (cm)	Jaw size (mm)	Minimal channel size (mm)	Price (USD)/No. in box	Material	Special features
MicroTech						
SureClip	235	8	2.8	1375/10	Stainless steel	
SureClip Mini	235	11	2.8	1242/10	Stainless steel	
SureClip PLUS	235	16	2.8	1492/10	Stainless steel	
SureClip MAX	235	17	2.8	1492/10	Stainless steel	
Lockado	235	11	2.8	1242/10	Stainless steel	
Lockado Plus	235	16	2.8	1492/10	Stainless steel	
Lockado MAX	235	22	2.8	1492/10	Stainless steel	
DAT Closure	165/235	15	3.2	350/1	Stainless steel	Two independently opening jaws
Steris						
Assurance	230	9, 11, 13, 16, 18	2.8	850/10		
Assurance Control	230	11, 16	2.8	7800/100		Short stem (7 mm) designed for retroflexion

opening and closing prior to deployment, (3) precise rotational control, and (4) a range of jaw widths for enhanced tissue approximation in a variety of clinical scenarios, ranging from 8 to 22 mm (Table 1).¹⁸

All TTS clips (Table 1) have a FDA indication for use “as a supplementary method for closure of GI tract luminal perforations less than 20 mm that can be treated conservatively.” TTS endoscopic clips are designed for compatibility with

a ≥ 2.8 -mm endoscope accessory channel, except for the Dual Action Tissue (DAT) Closure Device (Micro-Tech Endoscopy, USA Inc, Ann Arbor, Mich, USA) (Fig. 1), which requires a ≥ 3.2 -mm channel. Endoscopic clip delivery catheter lengths (155-235 cm) are available for gastroscopes, colonoscopes, and selectively for enteroscopes.¹⁹

The choice of endoscopic clip is dependent on the clinical circumstance, as each endoscopic clip has unique

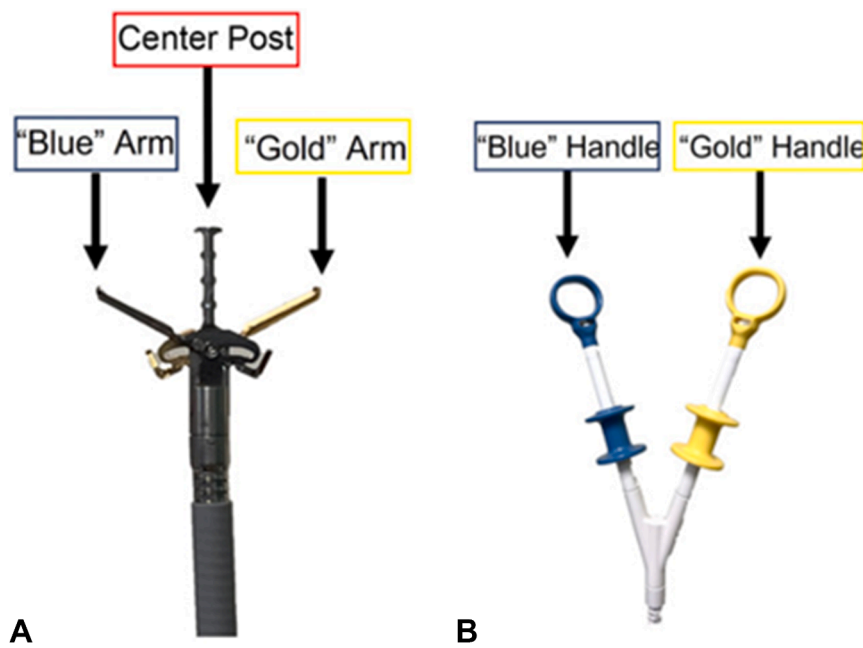


Figure 1. The Dual Action Tissue Clip has 2 arms that can open and close independently of each other (A), by use of 2 color-coded handles (B). Courtesy: Yang et al.¹⁹

physical and functional profiles. Variations in endoscopic clip rotatability, overshoot, open/close precision, and tensile/closure strength are noted as demonstrated in an ex vivo study comparing 5 endoscopic clips.²⁰ Moreover, endoscopic clip performance based on scope configuration in retroflexion, within the duodenal sweep, or across a duodenoscope elevator, are factors for endoscopic clip selection. TTS endoscopic clips are limited by a relatively small opening width, low closure strength, and depth of tissue capture that includes mucosa and submucosa but not full-thickness bowel wall.

Technical aspects

It is important for the endoscopy team to review the technical aspects of endoscopic clip placement and deployment since there are differences among the various endoscopic clips. The basic technique for TTS endoscopic clip placement includes multiple steps (Video 1, available online at www.giejournal.org). First, the endoscopic clip and delivery catheter is passed down the endoscope accessory channel in the closed position. Endoscope loops are reduced to achieve a straight scope position, when feasible. Endoscopic clips with short stems might be favored in tortuous endoscope positions, because their deployment is less affected by scope positioning, which in turn allows for easier deployment. Partial deflation of the intestinal lumen will help bring the edges of target tissue closer for capture within the endoscopic clip jaws. The endoscopic clip should be positioned close to the end of the endoscope for more precise control. Once the target and endoscopic clip position are optimized, the assistant opens the endoscopic clip by gently moving the slider or spool away from the

thumb ring on the handle. Most endoscopic clips can be opened and closed repeatedly before deployment. Endoscopic clips should be aligned perpendicular to the cut edge for perforation closure or approximation of EMR and ESD defects. This is typically accomplished by rotating the handle; however, one manufacturer develops endoscopic clips in which the clip orientation is achieved through rotation of the sheath while keeping the handle stationary. The endoscopy assistant may initiate endoscopic clip rotation, but the endoscopist may also rotate the sheath at the level of the accessory channel cap. It should be noted that the new DAT closure device is not rotatable. The jaws of this endoscopic clip open independently by 2 separate handle actuators.

Once the 2 edges of the intestinal defect have been approximated by endoscopic clip closure, the endoscopic clip is deployed by closing the handle forcefully, which most commonly requires using 2 hands to achieve adequate release. As the endoscopic clip is being deployed, there is typically an audible click and tactile feedback that indicates that the endoscopic clip has been fired. The Resolution 360 and 360 Ultra (Boston Scientific, Marlborough, Mass, USA) endoscopic clips, and the Olympus QuickClip 2 and Pro (Olympus America, Center Valley, Pa, USA) endoscopic clips need “reopening” of the handle to detach the endoscopic clip from the delivery catheter. It is important to follow the manufacturer instructions for use for each endoscopic clip.

Closure of defects larger than the open jaw span of the endoscopic clip can be achieved through tissue approximation starting at one end of the defect while sequentially placing endoscopic clips in a longitudinal or horizontal

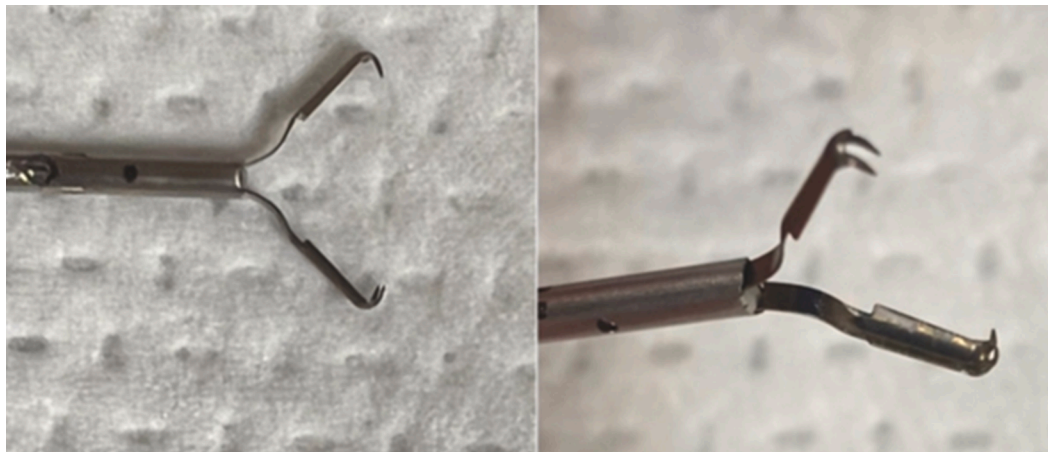


Figure 2. Anchor pronged clip. Note the distal modified anchoring prongs that minimize sliding of grasped tissue. Adapted from: Wei and Friedland.²¹

orientation in zipper fashion. A gentle advancement of the endoscopic clip catheter is suggested, because there is a slight endoscopic clip retraction on deployment. The initial endoscopic clip is placed just past the end of the defect, grasping normal tissue to achieve deeper tissue approximation. For perforations, it is important to place subsequent endoscopic clips in series with little to no gaps to create a leak proof closure. The use of a scope endcap or endoscopic clips with short tails may facilitate endoscopic clip manipulation when placing a series of endoscopic clips for larger defect closure. Pushing the tail of the clip with the cap can lift the mucosal defect and make placement of the following clips more efficient.

The Mantis endoscopic clip (Boston Scientific) (Fig. 2) has modified distal endoscopic clip anchoring prongs that minimize sliding of the grasped tissue, allowing for capture and dragging of 1 edge of the defect to the opposite side prior to endoscopic clip deployment. There are 2 techniques used for deployment of this anchor-pronged endoscopic clip, which are demonstrated in the video from Wei et al.²¹ The first, referred to as the “open technique,” captures normal mucosa along the edge of the defect with 1 prong in the open position, which then drags the edge to the other side of the defect for capture of the opposing edge prior to firing of the endoscopic clip. The second “closed technique” begins with capturing tissue on 1 edge of the defect by closing but not firing the endoscopic clip, followed by dragging of the captured edge to the opposite side of the defect. The endoscopic clip is reopened, and the opposing edge is captured prior to permanent firing.

TTS clips traditionally close defects up to 2 cm in diameter; however, the new Mantis endoscopic clip and DAT closure device have design advantages for tissue approximation, potentially allowing closure of defects up to 3 cm in diameter. Other, less commonly used advanced clipping techniques using a double-channel upper endoscope have also been described for closure of large defects. For example, an opened loop ligation device placed on normal

mucosa around the perimeter of the defect margin can be clipped in place and then closed to approximate the defect edges, in a technique referred to as the “tulip bundle” configuration.²² Another described technique involves using grasping forceps to first approximate the defect edges, followed by placement of a TTS clip.²³

TTS endoscopic clips are not designed for use with a duodenoscope, although success has been reported for hemostasis and perforation management following sphincterotomy. There may be a technical advantage to using clips with short tails (Duraclip; ConMed, Largo, Fla, USA) for this purpose, or in similar situations with severe endoscope angulations like with through an enteroscope.²⁴

OVER-THE-SCOPE CLIPS

OTS clips close defects larger than what can be achieved with traditional TTS clips but require temporary removal of the endoscope for assembly of the delivery system prior to deployment. The first clinical series in 2007 reported the use of OTS clips for 11 patients needing hemostasis and deep GI wall defect or perforation closure.²⁵ OTS clips in the USA are FDA cleared for endoscopic marking of lesions, hemostasis, and closure of GI tract luminal perforations <20 mm that can be treated conservatively.²⁶

Additional off-label applications for OTS clips include other nonperforation transmural tissue defect closures (fistulas and leaks), closure of mucosectomy sites (EMR, ESD), mucosotomy sites (peroral endoscopic myotomy, or POEM), stent fixation, and closure of natural orifice transluminal surgery (NOTES) gastrotomies and other full-thickness resections with or without surgical (laparoscopic) support.²⁷⁻²⁹

Technical aspects

Two OTS clips are commercially available in the United States: the OTSC system (Ovesco Endoscopy AG, Tübingen, Germany) and the Padlock (Steris Endoscopy, Mentor, Ohio, USA) (Fig. 3).³⁰ Both OTS clips are mounted in a



Figure 3. OTSC (left) versus the Padlock clip (right), both in their deployed configurations. Courtesy of: Al-Bawardy et al.³⁰

TABLE 2. Over-the-scope clips and accessories

Manufacturer	Outer diameter (mm)	Scope diameter (mm)/channel diameter	Sheath length (cm)	Cap depth (mm)	List price (USD)	Type of tip
Ovesco						
Mini (10 mm)	14.6	8.5-10	165	6	438	a, t
11 mm	16.5	8.5-11	165	3,6	438	a, t
12 mm	17.5	10.5-12	165/220	3,6	438	a, t, gc
14 mm	21	11.5-14	220	3,6	599	a, t
Accessories						
Twin Grasper	2.6	3.2	165/220	N/A	619	N/A
Anchors	2.4	3.2	165/220	N/A	441	N/A
remOVE Impulse Generator	N/A	N/A	N/A	N/A	3250	N/A
remOVE DC Cutter Sets	2.6	2.8	220	N/A	399	N/A
Steris						
Padlock	16	9.5-11	177	10	599	N/A
Padlock Pro	19	11.3-14	177	4-19	599	N/A

a, Atraumatic; gc, gastric closure; N/A, not applicable; t, traumatic; USD, United States Dollars.

preassembled open position on a clear applicator cap, which attaches to the end of a gastroscope or colonoscope. The OTS endoscopic clips are much larger than TTS endoscopic clips and capture a larger and deeper amount of tissue, often with serosa-to-serosa apposition. More research has been performed using the OTSC system than the Padlock endoscopic clip, although both have been better demonstrated at prevention of recurrent bleeding than defect closure.

OTS clips are available in gastroscope and colonoscope lengths. The OTSC system has 4 sizes for the applicator cap (Table 2) based on compatibility with the outer scope tip diameter (mini, 11, 12, and 14) and 3 types of teeth for the clip itself (a, t, and gc).³¹ The “a” endoscopic clip has “atraumatic” teeth, which are blunted for tissue compression, and is mainly used for hemostasis. The “t” endoscopic clip has “traumatic” teeth, consisting of small spikes at the

tip for compression and anchoring of tissues, and is recommended for use in the small intestine or colon, which have thinner walls. The “gc” (gastric closure) endoscopic clip has teeth with longer spikes and is recommended for closure of defects in the thicker gastric wall. There are 2 cap depths, 3 and 6 mm, and their use depends on how much tissue is intended to be captured (Table 2). A 6-mm cap depth may be preferred to capture more tissue for perforation closure. Many times, the target tissue is captured with a suction technique, but accessories may be necessary for tissue traction. There are 2 accessories used to assist with tissue retraction into the OTSC system: the Twin Grasper (Ovesco Endoscopy AG, Tübingen, Germany) and Anchor (Ovesco Endoscopy AG). The Twin Grasper is intended to approximate opposing edges of a perforation defect. It has 2 jaws that open and close independently. The Anchor is a three-pronged device used to pull fibrotic tissue into the

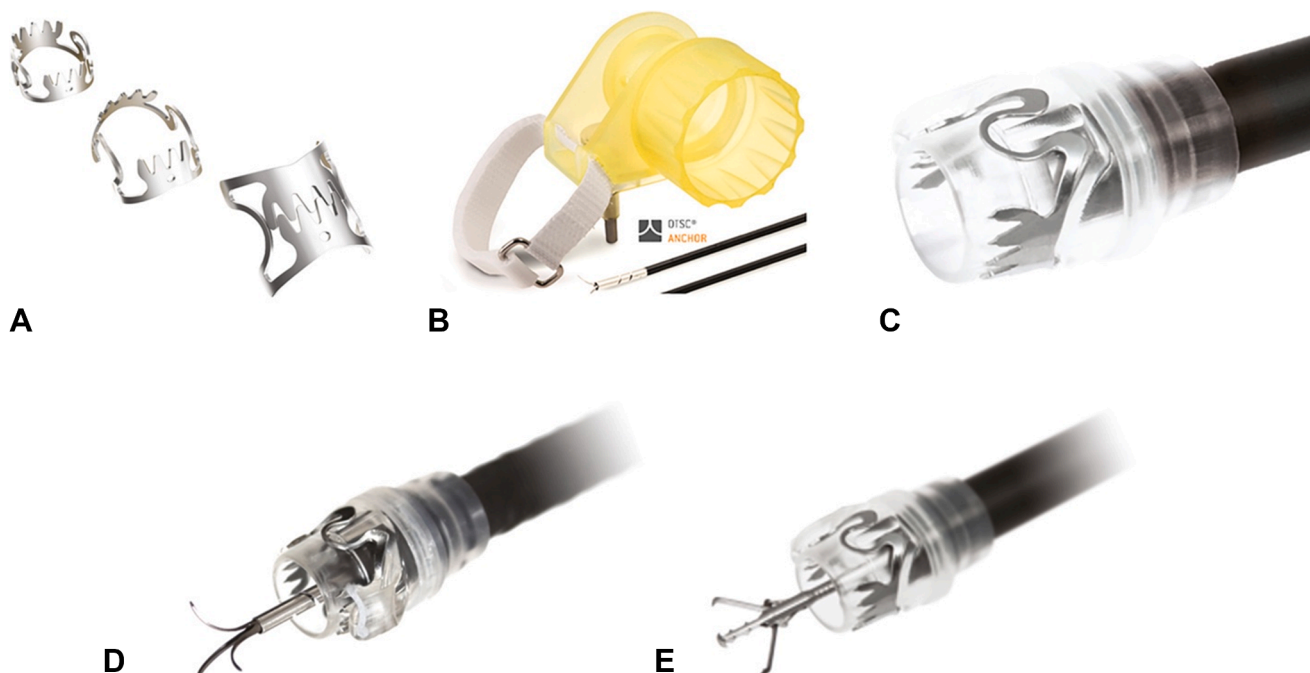


Figure 4. The over-the-scope clip (OTSC) system with accessories, including the clip itself (A), handwheel (B), clip mounted on scope cap (C), Anchor (D), and Twin Grasper (E). Courtesy of: Schurr et al.³²

cap.^{29,32} It is available in 2 versions for stomach (165 cm length, 12 mm needle width, and 4 mm needle depth) and colon (220 cm length, 9 mm needle width, and 2-2.5 mm needle depth) retraction. The OTSC system endoscopic clips are released by mechanism like that of an endoscopic band ligator (Fig. 4).³² The rotating handle is connected to the endcap by a thread passed through the accessory channel, which is then put under tension by rotating the handle clockwise leading to deployment of the endoscopic clip.

The Padlock endoscopic clip is an 11-mm hexagonal nitinol ring with 6 internally projecting spikes designed to retract tissue into the clip upon deployment.³³ Two cap sizes with delivery catheters of 177 cm length are available for diagnostic (Padlock: for endoscopes of 9.5-11 mm diameter) and therapeutic (Padlock Pro-Select: for endoscopes of 11.3-14 mm diameter) upper endoscopes and colonoscopes. The standard device has a tissue chamber depth of 10 mm whereas the depth ranges from 4 mm to 19 mm for the Pro-Select clip, depending on the diameter of the scope. The Padlock clip is deployed by depressing a button on the control handle, which is connected to the cap/endoscopic clip by an actuation cable located outside and alongside the shaft of the scope. There are no recommended accessories for retracting tissue into the Padlock cap.

ENDOSCOPIC SUTURING

Endoscopic suturing has emerged as an important tool in the management of GI leaks, perforations, and fistulas. Unlike

traditional TTS clips, endoscopic suturing can perform full-thickness approximation and closure of large defects because the technique is not limited by the size of the defect. Previous suturing systems no longer available include the Endocinch (C.R. Bard, Murray Hill, NJ, USA), T-Bar (Cook Medical, Bloomington, Ind, USA), and Eagle Claw (Olympus America), which will not be discussed in this review. Currently commercially available flexible endoscopic suturing systems include the over-the-scope suturing (OTSS) system, OverStitch (Boston Scientific), and the through-the-scope suturing (TTSS) system, X-Tack (Boston Scientific).

OVER-THE-SCOPE SUTURING

The commercially available OTSS system (OverStitch) received FDA 510k clearance in 2008 for use as an endoscopic suturing system to approximate tissue. It is widely used for luminal GI defect closure, closure of entry sites for third space endoscopy, and enteral SEMS fixation, as well as for several bariatric endoscopy-related applications. OTSS allows for full-thickness closure by incorporating the muscularis propria to create a more stable construct for tissue closure.³⁴

Technical aspects

The Overstitch device consists of 3 main components: (1) the suturing platform itself; (2) the anchor exchange catheter, along with the anchor and affixed suture; and (3) the suture cinch (Fig. 5).³⁴ It is compatible with double-channel therapeutic gastroscopes. The endplate of the suturing platform attaches to the therapeutic

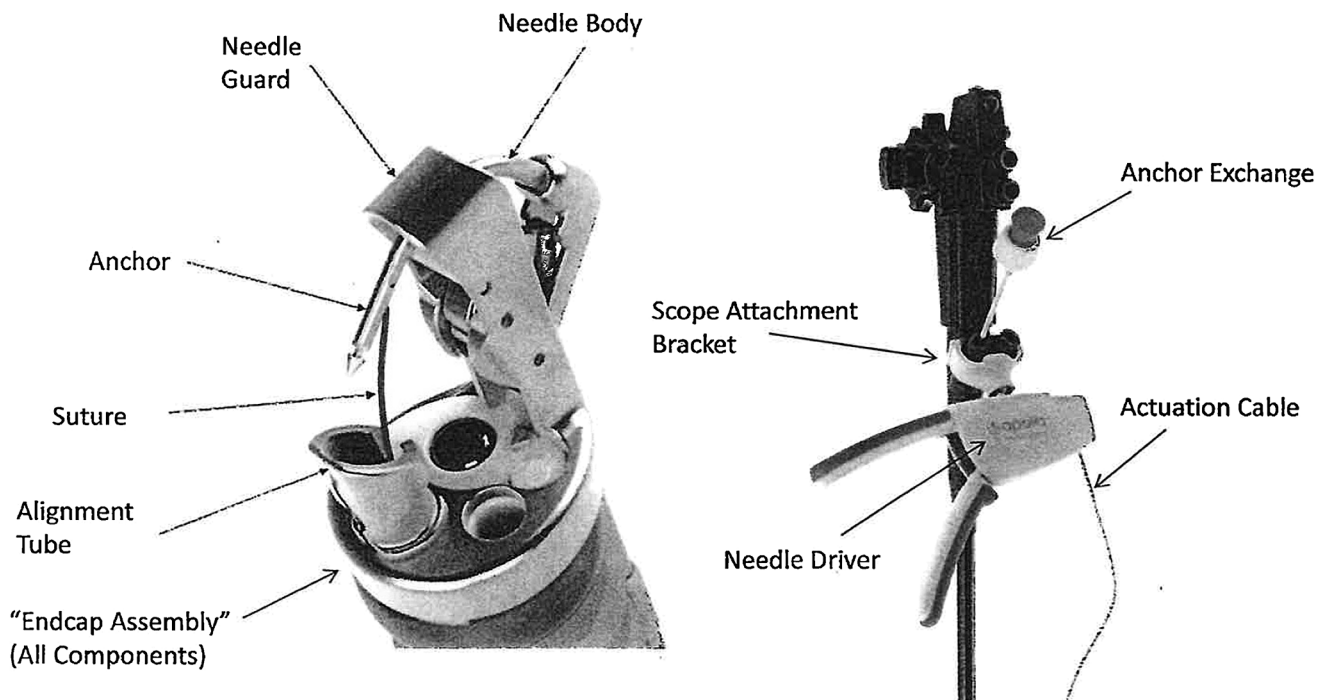


Figure 5. The components of the over-the-scope suturing platform, Overstitch, including the endplate (left) and control handle (right). Courtesy of Boston Scientific.

channel of the double-channel gastroscope and connects to an actuation cable that runs alongside the gastroscope and is attached to a control handle with a lever (called the needle driver). The needle driver attaches to the lip of the gastroscope's accessory ports and actuates the opening and closing of the needle body. The OTSS system comes with a flexible metallic catheter, called the anchor exchange catheter, which fits within the 3.7-mm accessory channel of the gastroscope. The catheter allows for transfer of the anchor and affixed suture between the needle body and the anchor exchange catheter, facilitating additional plications and various interrupted or running suture patterns (Fig. 6).³⁵ The last component of the OTSS system is the suture cinch, which provides an endoscopic "knot" and cuts the remaining suture. To facilitate larger, or more often full-thickness, tissue bites, a corkscrew-like device called the tissue helix is also available (Fig. 7). The use of a mixed-tooth grasping forceps as an alternative to the tissue helix has also been described.³⁶ The tissue helix is a catheter-based retractor that fits through the 2.8-mm accessory channel of the double-channel gastroscope. Its corkscrew design allows it to be drilled into tissue by clockwise rotation, capturing tissue within the helix. The tissue helix can then be retracted to facilitate full-thickness bites. A counterclockwise rotation of the tissue helix releases the captured tissue prior to subsequent plications. The full step-by-step guide for use of the OTSS system is viewable in several instructional videos available on the vendor website.³⁷

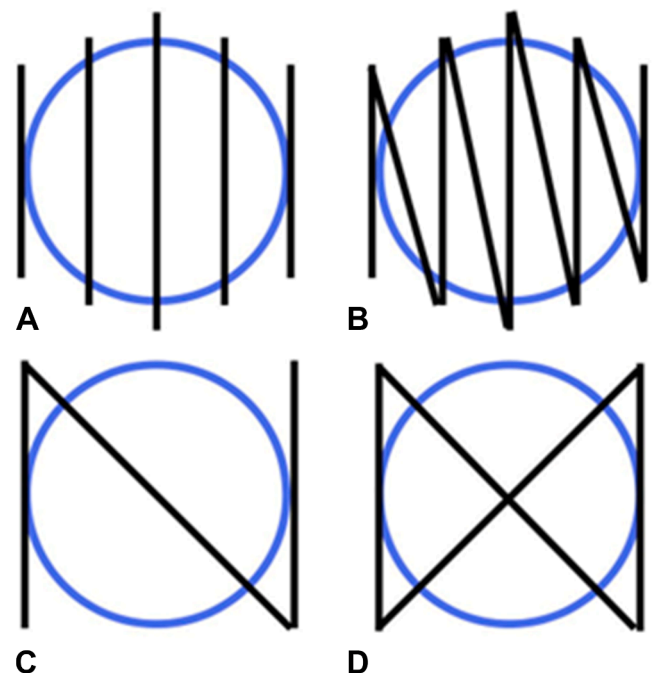


Figure 6. Types of suture patterns, including interrupted (A), running (B), Z-shaped (C), and figure of 8 (D).

In 2017, the manufacturer of the OTSS system received 510k clearance for a related suturing device that does not require a double-channel gastroscope, called the Overstitch Sx. Like the original OTSS system, the single-channel OTSS

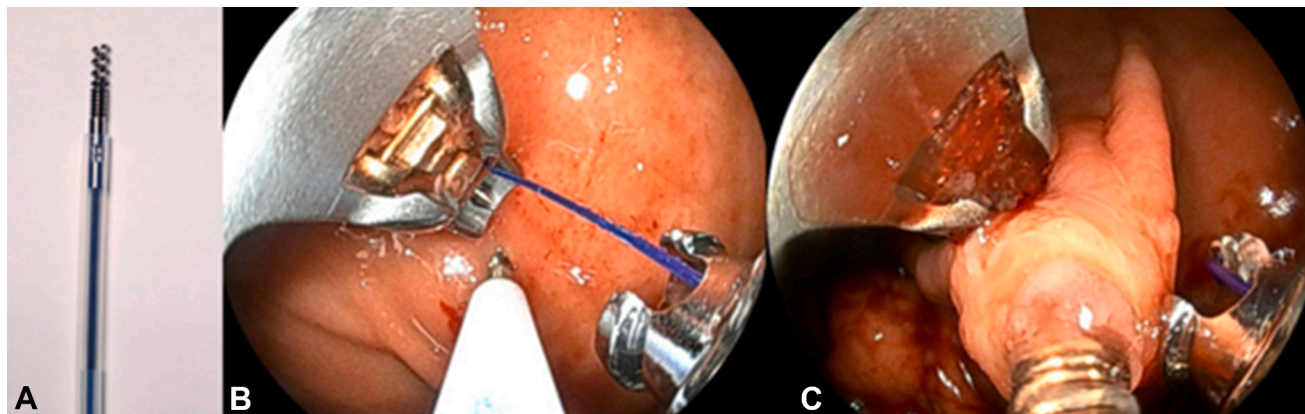


Figure 7. The tissue helix (A). The tissue helix capturing gastric tissue (B) and retracting it into the jaws of the over-the-scope suturing platform (C). Reproduced from Wooley et al.³⁶

system is a flexible endoscopic suturing system that allows for tissue approximation. Although the original OTSS system was compatible with only a double-channel therapeutic gastroscope, the single-channel system fits onto the outer shaft of a standard gastroscope and is thus compatible with 20 standard single-channel gastroscopes across 4 different manufacturers including Olympus, Pentax (Pentax Medical, Tokyo, Japan), Fujifilm (Fujifilm, Lexington, Mass, USA), and Storz (Storz, Tuttlingen, Germany).³⁸ Neither system is compatible with colonoscopes. The control handle is fixed near the working channel and contains 2 ports: 1 for the anchor exchange catheter and the other for the tissue helix. The accessory channel of the gastroscope is not required for use. The technical method for suturing is identical to the standard OTSS system.³⁸ Even more recently, in 2023, the manufacturer received 510k clearance for an updated single-channel OTSS system, called the Overstitch NXT. Like the original iteration, the updated single-channel OTSS system is a flexible endoscopic suturing system intended for tissue approximation that is designed to fit over a standard, single-channel gastroscope. In comparison, assembly of the newer device has been streamlined. In addition, the updated single-channel OTSS system comes equipped with a pull-string mechanism that can be tightened to incrementally enhance scope retroflexion and maneuverability up to 210 degrees of retroflexion, which has implications for difficult-to-suture locations (eg, the gastric fundus) (Fig. 8).³⁹

THROUGH-THE-SCOPE SUTURING

In December 2020, the X-tack Endoscopic HeliX Tacking System, or X-tack (Boston Scientific) was FDA-approved for soft tissue approximation in procedures. X-tack, unlike other suturing systems, functions through a 2.8-mm working channel and does not require the endoscope to be removed for setup or deployment. It is available in 2 lengths for compatibility with all standard colonoscopes (235 cm)



Figure 8. The Overstitch NXT OTSS system, demonstrating 210-degree retroflexion using MaxFlex. The incremental retroflexion is achieved using a pull-string mechanism attached to the control handle (not pictured). Courtesy of Boston Scientific.

and gastroscopes (155 cm). Small studies and case reports demonstrate variable closure efficacy with the TTSS system for perforations, leaks, fistulas, mucosal resection defects, and stent fixation.⁴⁰⁻⁴³ The TTSS system has the advantage of closing larger and more irregular defects that would be challenging to close with TTS clips, as well as defects in difficult-to-reach locations such as the right side of the colon and small intestine that would otherwise be outside the reach of a therapeutic gastroscope for standard OTSS. However, its effectiveness is less than that of the OTSS system, and it often requires the use of adjunctive closure techniques (eg, endoscopic clips) for complete closure.

Technical aspects

The X-tack consists of a mounting platform that attaches to the handle of an endoscope, a push catheter, a

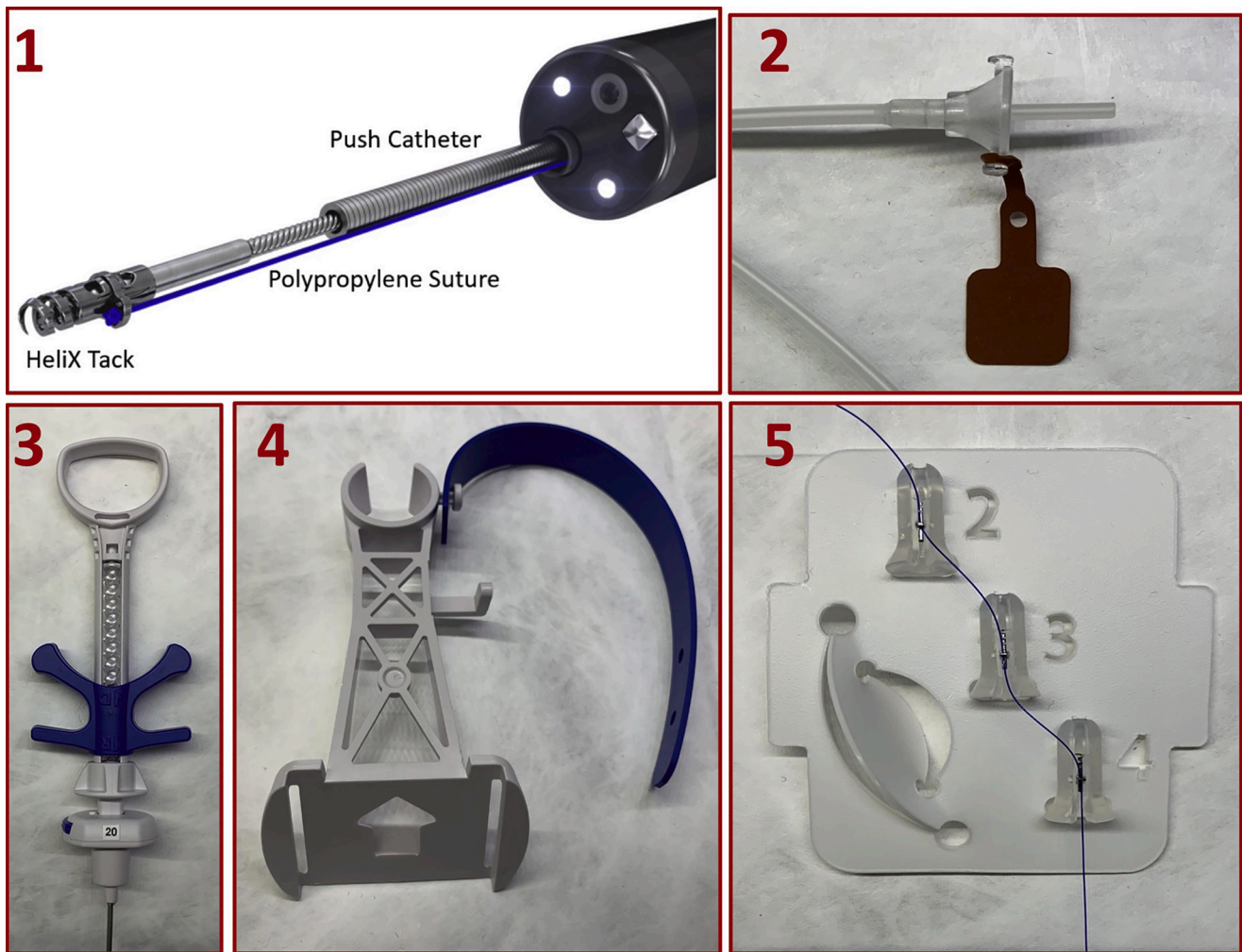


Figure 9. The X-tack device, including the push catheter and associated tack (1), the channel liner (2), the Persian Drill-based deployment handle (3), the mounting platform (4), and the pre-strung helical tacks (5). Reproduced from Hernandez-Lara et al.⁴⁴

preloaded helical tack within a protective liner that is placed down the working channel of the endoscope, and 3 additional MRI-conditional 5-mm-length steel helical tacks pre-strung on a 3-0 propylene suture (Fig. 9).⁴⁴ Each tack is applied individually and sequentially, as demonstrated in the video by Hernandez-Lara et al.⁴⁴ The delivery mechanism is a Persian Drill-based, pull-back finger slider that translates linear motion into corkscrew, clockwise rotation of the tack, allowing it to penetrate tissue until adequate capture of tissue is achieved. Once this is done, the tack is released. In contrast to other endoscopic closure technologies, suction is not applied to partially collapse the intestinal lumen prior to tack application because a distended lumen is preferred for tissue capture. Once the initial tack is deployed, the delivery catheter is removed, another helix tack is connected and passed through the working channel, and the tack is deployed on the opposite side of the defect. Like with OTSS, several closure patterns have been described depending on the

shape of the defect and desired strength of tissue apposition, including Z-shaped and figure-of-8. Once the 4 tissue tacks are placed, a cinch (identical to that used for Overstitch) is passed in a monorail manner over the propylene suture. Tension is applied on the suture to bring the 4 tacks together and the cinch is deployed. The suture cinch selected is unique in length for either the gastroscope or colonoscope.

TISSUE SEALANTS

Chemical closure devices involve injection of polymer liquid into a fistula with the goal of creating a solid plug. Eventual granulation tissue and overgrowth with epithelialization provides long-term closure of the leak or fistula. Tissue adhesives have been reviewed in prior ASGE Standards of Practice and Technology documents.^{45,46} In summary, 2 categories of chemical closures exist. The first is

cianoacrylate (CYA) glue and the second is fibrin sealants. Cardiac septal occluders (CSOs) are another form of tissue sealant through a mechanical closure device.⁴⁷

CYANOACRYLATE GLUE

CYA glues come in various chemical formulations with varying lengths of an alkyl group that affects polymerization times, which can be further slowed down with the addition of lipiodol, an agent that makes the injectate radiopaque when fluoroscopic imaging is used to facilitate delivery. CYAs polymerize quickly upon contact with anions and are not broken down by digestive enzymes.⁴⁸ CYA formulations have an FDA indication for prevention of leaks from colorectal anastomoses and wound closure but are used off-label for endoscopic applications.⁴⁵

FIBRIN SEALANTS

Fibrin sealant preparations are commercially available and require thawing to room temperature prior to use because they are stored frozen. The products are supplied in a specialized double-barreled syringe, 1 containing fibrinogen and factor XIII and the other an activation solution containing human thrombin. The 2 components can be delivered to the target location through a specialized double-lumen catheter passed down an endoscope channel by depression of the syringe plunger, resulting in activation when the 2 components mix upon extrusion.⁴⁵

CARDIAC SEPTAL OCCLUDERS

CSOs are occlusion devices (Amplatzer; AGA Medical Group, Plymouth, Minn, USA) used for the minimally invasive treatment of cardiac septal defects, effectively eliminating blood flow across an atrial or ventricular cardiac congenital defect. They have been used off-label to treat refractory GI fistulas (Fig. 10).^{47,49} CSOs are biflated, dumbbell-shaped devices made of nitinol and a polyester coating, with a deployed appearance similar to that of a lumen-apposing metal stent but without the central lumen. They come in various flange sizes that range from 3 to 38 mm in diameter. The appropriate device configuration can be selected based on the length and diameter of the fistula tract, which can be measured using a conventional dilating balloon. The device is then placed with the flanges on both ends of the fistula tract causing occlusion and leading to eventual permanent tissue ingrowth and overgrowth.

Endoscopically, CSOs are deployed over a standard guidewire under fluoroscopic guidance. CSOs are constrained within a delivery catheter up to 80 cm in length, and thus cannot be placed through the accessory channel of an endoscope, restricting deployment to GI sites within reach of the catheter. However, recent case reports have

described backloading of the CSO device on a 10F stent delivery system allowing deployment via a therapeutic gastroscope.^{50,51}

CLINICAL OUTCOMES FOR ENDOSCOPIC CLOSURE

Endoscopic closure of GI defects is largely dependent on the etiology, location, size, and chronicity of the tissue injury. Acute luminal defects include perforations and surgical anastomotic fistulas, which are often iatrogenic and have a greater likelihood of successful long-term closure compared with chronic fistulae.^{3,52-54}

ENDOSCOPIC CLIPPING

Through-the-scope clips

TTS clip closure is sufficient to achieve adequate healing of iatrogenic perforations despite the relatively superficial tissue grasp, which is limited to the mucosa and submucosa.⁵⁵ A systematic review, including 4 large cohort studies totaling 466 patients with acute iatrogenic GI perforations closed endoscopically, demonstrated successful closure in 90.2% (95% CI, 87%-93%) of cases using TTS clips and in 87.8% ($n = 58$; 95% CI, 78%-95%) using OTS clips.³ The majority of perforations closed by TTS clips were likely small perforations after mucosectomy (EMR and ESD), as perforation size was not reported in the studies. The overall success (combined TTS and OTS clips) rates by location were as follows: gastric (98.4%), colon (83.8%), esophagus (92.9%), and duodenum (88.2%).

Clinical success rates for colon perforation closure range from 74% to 95% and conversion to surgery ranges from 22% to 26%.^{3,56,57} Surgical intervention, when required following failed endoscopic closure, leads to longer hospital stays and more frequent AEs such as abscess formation and wound infection.⁵⁶

TTS endoscopic clips alone are generally not ideal for closure of leaks or fistulas given their limitations, including small size, relatively low closure force, and inability to appose deep tissue that may be chronically inflamed and fibrotic. However, they may be used as a supplementary technique in these clinical scenarios.⁴ To date, no studies have provided clinical efficacy data using newer, larger-jaw (>16 mm) TTS endoscopic clips or the Mantis or DAT endoscopic clips for closure of GI defects.⁵⁸

Over-the-scope clips

A systematic review of 24 studies including 466 patients with iatrogenic acute intestinal perforations of the GI tract demonstrated successful closure with OTS endoscopic clips in 87.8% of cases.³ Another systematic review of 19 studies for leak closure with a total of 319 patients showed an overall technical success rate and clinical success rate of 91% and 84%, respectively.⁵⁹ A systematic review of OTS

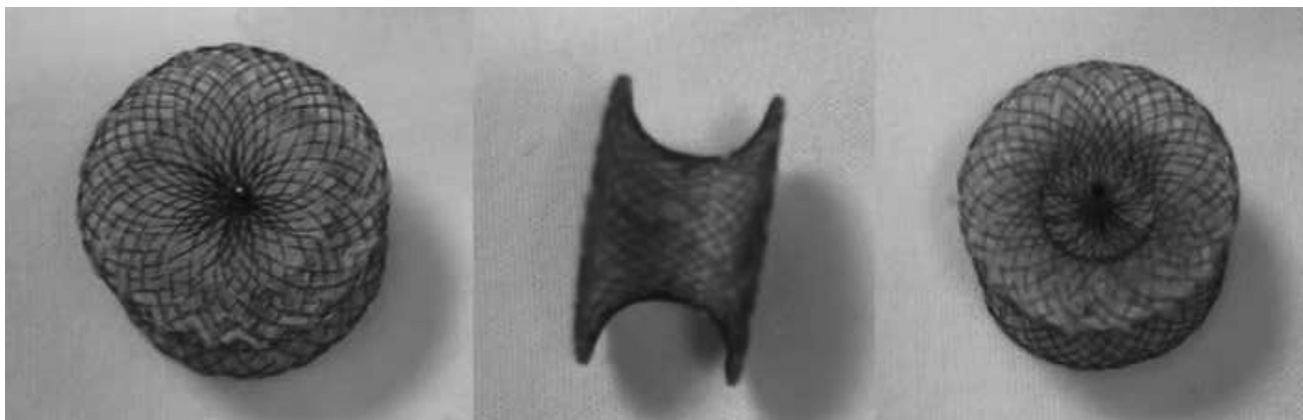


Figure 10. Cardiac septal occluders (CSOs). Courtesy of: Hourneaux de Moura et al.¹²⁶

endoscopic clip closure included 3025 patients for a variety of hemostatic and defect closure indications.²⁹ OTS endoscopic clip closure of acute intestinal perforations ($n = 468$) noted technical success rates and clinical success rates of 95.5% and 85.3%, respectively. Surgical intervention to achieve complete closure of perforation sites after OTS endoscopic clip placement was required in 9.4%.²⁹ Adverse events were observed in 2.1% of endoscopic clip deployments. The same review assessed anastomotic leak closure in 391 patients with OTS endoscopic clips, reporting a technical success rate of 86.7%, and a clinical success rate of 72.6%. Surgical intervention after OTS endoscopic clip placement was required in 7.4%.²⁹ A small series of 26 patients reported the use of OTS endoscopic clips to treat perforated peptic ulcer disease. The clinical success rate was 100% without any need for surgical intervention, with a 30-day follow-up and no reported AEs.³¹

Endoscopic treatment of intestinal fistulas has a lower success rate compared with acute perforation closure because of the extended duration of the process, tract fibrosis, and poor vascularization of the tissue. A review including 24 studies totaling 301 patients found long-term overall success rates for treating GI perforations, leaks, and fistulas with OTS endoscopic clips ranging between 42% and 100%, with a pooled success rate of 73%. However, the success rate was dependent on the type of defect, because closure of endoscopic perforations had a 90% success rate compared with 59% for chronic leaks and fistulas.⁶⁰ A systematic review totaling 622 patients with intestinal fistulas found a technical success rate and clinical success rate of 92.8% and 55.8%, respectively.²⁹ Another review of 20 studies including 437 patients noted a technical success rate of 80% and clinical success rate of 48%.⁵⁹ A retrospective review included 47 patients treated with OTS endoscopic clips for fistulas secondary to a variety of etiologies, including prior percutaneous endoscopic gastrostomy (PEG)/percutaneous endoscopic jejunostomy (PEJ) ($n = 12$), post-Roux-en-Y

gastric bypass (RYGB) gastrogastic ($n = 8$), Crohn's disease ($n = 4$), nonbariatric surgery ($n = 11$), and diverticulitis ($n = 3$). The initial technical success rate was 89% (42/47), but the clinical success rate was less robust at 53% (25/47).⁶¹ Of note, in those with fistula recurrence who underwent a subsequent endoscopic examination, the OTS endoscopic clip was found adjacent to the fistulous tract in 84% of cases (16/19).

OTS endoscopic clips have also been used to successfully to close mucosotomy sites for third-space endoscopy. One study showed that closure of entry sites for POEM (esophageal and gastric) was faster (50% reduction) with OTS versus TTS clipping. On average, 1 OTS endoscopic clip was used per closure site versus 5 to 6 TTS endoscopic clips. AEs occurred more commonly with the TTS endoscopic clips compared with OTS endoscopic clips for both esophageal (21.7% vs 13%; $P = .01$) and gastric POEM (7.7% vs 0%; $P = .02$).⁶²

ENDOSCOPIC SUTURING

Over-the-scope suturing

The use of OTSS for perforation closure was initially described in several small studies.⁶³⁻⁷² In 2014, a case series reported the successful closure of 3 esophageal perforations of various etiologies (spontaneous, food impaction, post-TEE) using OTSS.⁷² Long-term follow-up was not reported. In another case series of 9 acute perforations, technical and clinical success with OTSS repair was noted in 89% (8/9) and 88% (7/8) of cases, respectively.⁵⁴ The sole technical failure occurred in an acute surgical perforation from paraesophageal hernia repair, and the lone clinical failure in an iatrogenic perforation from peroral pyloromyotomy. The largest series to date has been a multicenter, retrospective review of 122 patients who underwent OTSS for luminal defect closure. In this series, 20 procedures were performed for an indication of acute perforation with a 93% clinical success rate.⁷³

Unlike acute perforations, fistulas and leaks range from subacute to chronic in duration and contain some degree of tract maturation, epithelialization, and fibrosis, resulting in a greater challenge when attempting durable endoscopic closure. Gastrocutaneous fistula closure, such as following PEG tube placement, has been described using OTSS in several small case series and reports with high levels of immediate technical and clinical success.⁷⁴⁻⁷⁶ Long-term success is likely lower. For instance, Mukewar et al⁷⁷ reported a multicenter series of 56 patients who underwent endoscopic fistula closure using OTSS, including 43 (77%) postoperative fistulas and 16 (29%) fistulas that had failed prior closure attempts with TTS clips and thermal therapy. Immediate closure was achieved in all patients. However, persistent closure at 12 months was observed in just 22.4% of patients, with an even lower rate (17.1%) seen in those with gastrogastic fistulas. Of note, 17 patients required an additional endoscopic procedure after initial closure, highlighting the limitations of single-session fistula closure. Of these, 4 patients went on to achieve ultimate clinical success. Another multicenter series of 40 patients with mostly gastrojejunal anastomosis (55%) and gastric (30%) fistulas reported long-term success rates of endoscopic closure in 80% of cases, but follow-up was limited to just 68 days. The success rate of OTSS for 15 cases of postoperative leaks was 27%.⁷³

Overall, OTSS has a growing body of literature supporting its use in the closure of perforations, fistulas, and leaks. Available data support its effectiveness for closing EMR and ESD-related perforations and mucosal defects, regardless of size. Efficacy of OTSS to durably close fistulas and leaks is lower (27%-80%), and alternatives, such as internal drainage, endoscopic vacuum therapy, polymers, and others, should be considered as part of a multidisciplinary discussion.

Through-the-scope suturing

A retrospective, multicenter study described the use of TTSS in 93 patients across a variety of indications, with the most common indication (58% of cases) being for mucosal defect closure after EMR or ESD.⁴¹ Closure of full-thickness defects, such as perforations (3.2%) or fistulas (11.8%), were uncommon. TTSS use was distributed throughout the GI tract, including in the colon (51%), small bowel (23.7%), stomach (16.1%), and esophagus (8.6%). The mean defect size was 41.6 ± 19.4 mm. Technical success was 89.2%, although supplemental closure was needed with TTS clips in 24.7% of patients. There are limited long-term data on the use of TTSS for closure of perforations, fistulas, and leaks. In the study by Mahmoud et al,⁴¹ follow-up was available in 12 of 93 (13%) patients. In 3 patients who underwent initial closure for post-EMR defects, all showed well-healed defects with retained tack and suture material at up to 3 months. Two patients who underwent closure for fistulas showed resolving fistulas at 2 and 4 months, respectively. Nevertheless, TTSS remains an attractive alternative to standard TTS clips

because of its ability to close large or irregular defects in the proximal colon and small bowel, which are often outside the reach of OTSS.

TISSUE SEALANTS

Cyanoacrylate glue

CYA glue is perhaps the oldest treatment of intestinal leaks and fistulas, with the first case published in 1983.⁷⁸ Most subsequent reports describe the intraoperative use of CYA. However, several groups have also reported experience with endoscopic delivery.^{79,80} Overall, the data on defect closure with CYA glue are limited to small case series and heterogenous systematic reviews with short follow-up, making it difficult to determine its overall efficacy for this purpose. A systematic review totaling 14 studies with 203 patients demonstrated a success rate of 81% for closure of predominantly postsurgical foregut and hindgut fistulas. However, the size of the fistula, use of supplemental (eg, percutaneous) closure techniques, and length of follow-up were not reported.⁸⁰

Fibrin sealants

The endoscopic use of fibrin sealant as a monotherapy for leaks and fistulas of various etiologies has been described since at least 2004.⁸¹⁻⁸⁹ A systematic review totaling 10 studies with 63 patients reported closure rates between 92% and 100% using fibrin sealant monotherapy for treatment of postbariatric surgery leaks and fistulas.⁹⁰ The median time between bariatric surgery and fibrin sealant application was 12.5 days (range, 1-144 days), but the size of the fistulas was not reported. There was notable heterogeneity in both the number of treatment sessions needed (1-14 sessions) and interval between sessions (2-14 days). Follow-up was reported in 5 studies and ranged from 3 to 42 months.⁹⁰

As an adjunct to treatment with fibrin glue, polyglycolic acid (PGA) sheets can be attached to the mucosal defect using TTS clips to serve as a scaffolding that in turn binds to fibrin glue. In 1 report, 2 patients with leaks (1 postoperative, 1 related to a perforated ulcer) were treated with combination PGA sheet application and fibrin sealant, with successful defect closure seen at 2 months and 12 days, respectively.⁹¹ Clinical success in closing anastomotic dehiscence and iatrogenic perforation after transesophageal echocardiogram with the use of PGA sheets and fibrin glue has likewise been reported.^{92,93} In a series of 10 patients with postesophagectomy leaks that were treated with combination PGA sheet application and fibrin glue, successful closure was achieved in all patients.⁹⁴ The mean number of treatments was 1.7 with a median time to resumption of oral intake of 31.6 days following initial treatment.

The use of adipose-derived stem cells as an adjunct to fibrin glue has also been described. A clinical trial assessed the use of fibrin sealant along with adipose-derived stem

cells in the treatment of postoperative enterocutaneous fistulas. In this trial comprising 6 patients with primarily inflammatory bowel disease-related postoperative fistulas, there was a 100% closure rate at 24 weeks following combined percutaneous and endoscopic treatment with adipose-derived stem cells and fibrin sealant.⁹⁵

Cardiac septal occluders

The use of a CSO to close an intestinal fistula was first reported in 2009 to treat a gastrocolic fistula following PEG placement.⁹⁶ A subsequent case report published in 2010 also noted successful closure of a postoperative gastrocolic fistula using a CSO.⁹¹ Since then, several case studies have highlighted the use of CSOs for the treatment of refractory gastrogastic, rectovesical, and rectovaginal fistulas.^{51,97,98} A recent systematic review assessed the use of CSOs for closure of intestinal fistulas or leaks across 19 studies and 22 patients.⁴⁷ Technical success was achieved in all patients. Furthermore, after a median follow-up of 33 weeks, durable fistula closure was observed in 17 of 22 (77.2%) patients. There were no identified clinical predictors of success.

Post-EMR/ESD defect closure

Particular mention is deserving of post-EMR/ESD defects, which are unique in the sense that they are often acute, iatrogenic, and at times anticipated during EMR/ESD. Previous ASGE technology documents have described the rates of perforation and other adverse events with EMR/ESD, as well as the use of routine endoscopic closure, such as with endoscopic clips.^{8,9} Multiple techniques exist for defect closure, with the chosen one(s) dependent on the anatomical location (stomach, small intestine, proximal colon, rectum, etc) and clinical circumstance (acute vs delayed), and operator skill set.

Several studies have established the effectiveness of clip closure for postresection mucosal defects.^{99,100} In one of the largest, 928 patients were randomized in a 2 × 2 fashion to EMR with either blended current (Endocut) or forced coagulation, and clip closure or no closure. Post-procedure bleeding occurred in 3.5% of patients in the clip group versus 7.1% in the control group.¹⁰¹ Consequently, endoscopic closure of postresection defects with TTS and OTS clips is currently recommended by international societies to reduce adverse events.¹⁰² Limitations of traditional TTS clips include their short blades, which limit grasping of deep tissue. With larger lesions, rates of successful closure following ESD has been reported to be as low as 40% to 61%. Higher rates are seen when endoscopic clips are used in conjunction with other devices.¹⁰³ Fewer studies are available evaluating newer clips, such as the DAT closure clip or Mantis clip. In a case series of 50 patients, 33 (66%) of whom were for post-EMR defect closure, successful closure was achieved in 32 of 33 (97%) patients. No patients experienced serious AEs related to the MANTIS clip.¹⁰⁴

Jinushi et al¹⁰⁵ compared standard TTS clips with OTS clip closure for mucosal defect closure after duodenal ESD. Of note, tumor size was not standardized between groups, with an overall larger tumor size in the OTS clips arm (20 mm vs 15 mm in the TTS clips arm). Complete closure was similar between groups with no significant difference in the rate of defect closure of AEs. Several other studies have demonstrated successful closure of postresection defects using OTS clips.^{106,107} For large defects, multiple OTS clips can be needed to achieve complete closure.¹⁰⁸ In several systematic reviews, the technical success of OTS clips was 89.1% and the clinical success was between 85.2% and 92.8%.^{29,109}

The use of OTSS for closure of acute perforations and large mucosal defects during EMR and ESD has also gained interest (Video 2, available online at www.giejournal.org).^{18,110} Endoscopic suturing allows for more reliable closure of large defects where the smaller size and jaw radius of TTS clips might be insufficient for adequate mucosal-to-mucosal closure. A retrospective review noted improved clinical success with OTSS compared with standard TTS clips for closure of 16 acute colonic perforations that occurred during diagnostic (2) and therapeutic (14) colonoscopy.⁶³ Therapeutic procedures comprised both EMR and ESD, with a combined mean defect size of 5.6 ± 4.8 mm. In a prospective study of 33 patients with large polyps (mean size, 5.38 ± 2.52 cm) throughout the GI tract who underwent post-ESD closure with OTSS, technical success was noted in 93.9% of patients, with complete closure in 90.9%. Twenty-five patients were discharged on the same day, with no cases of immediate or delayed perforation.³⁸ Another large, retrospective review of 55 patients also showed OTSS to reliably close post-ESD defects throughout the esophagus (6), gastroesophageal junction (2), stomach (30), and colorectum (17), with most patients (85%) being discharged same day.¹¹¹

TTSS has likewise been demonstrated to be safe and effective in closing post-EMR/ESD defects, with technical success rates >90% (Video 3, available online at www.giejournal.org).¹¹² However, supplemental closure (eg, with TTS endoscopic clips) can be required to achieve complete closure in a large proportion of cases. A meta-analysis evaluated the use of TTSS across a variety of indications, including closure of EMR (34.4%) and ESD (26.6%) defects. The technical and clinical success (defined as complete closure without other modalities) rates were 96% and 74.8%, respectively. Adverse events were noted in 7.3% of cases, including bleeding (1.7%) and perforation (1.1%).¹¹³ Examples of TTSS to close various iatrogenic defects can be seen in the video(s) available from Zhang et al.¹¹⁴ In a comparison with OTSS, Agnihotri¹¹⁵ randomized 40 patients (mean lesion size, 40.4–40.9 mm) who underwent ESD to closure with either OTSS or TTSS. Successful closure was similar between groups (85% in OTSS vs 90% in TTSS, *P* = .63). Three

failures occurred in the OTSS group because of failure to reach the lesion (2 proximal colon, 1 gastric fundus) highlighting the role for TTSS. In a systematic review totaling 449 patients, the pooled rates of complete defect closure after EMR and ESD were 99.2% and 92.1%, respectively.¹¹⁶

There have been few reports of using tissue sealants to treat post-EMR/ESD mucosal defects and even less controlled trials and meta-analyses. Seehawong et al¹¹⁷ described the use of fibrin glue with polyglycolic acid sheets to repair a 30-mm esophageal defect, with success. In a meta-analysis of 25 patients (fibrin = 10, CYA glue = 15) who underwent tissue sealant repair, fibrin had a technical success of 100%, with 80% of patients demonstrating persistent closure at follow-up endoscopy after 2 weeks. In the CYA group, there were no cases of postprocedure bleeding, compared with 2 in the endoscopic clips alone group.¹¹⁸

SAFETY CONSIDERATIONS

Endoscopic clipping (TTS and OTS clips)

The AE rate in a review of TTS endoscopic clips was 2.1% (40/1942). The most common AEs were incorrect site of placement, 27.5% (11/40); perforation, 22.5% (9/40); bleeding, 25% (10/40); and infection, 25% (10/40). There was no mortality associated with these adverse events.²⁹

Adverse events with OTS endoscopic clips may occur at each step of the placement process. The spectrum of adverse events includes finger injury to the user during device setup, as well as intestinal laceration and perforation in the patient when attempting to advance an OTS endoscopic clip across areas of physiologic narrowing such as the upper or lower esophageal sphincters, and premature deployment in an accidental location (including the tongue). Entrapment of accessory devices (OTS grasper and anchor) within the teeth of the endoscopic clip can occur when the devices are not adequately retracted prior to endoscopic clip deployment. More serious adverse events, some requiring surgical intervention, have been reported. These include small-bowel fixation of opposing intestinal walls leading to bowel obstruction or pyloric stenosis and capture of extrinsic structures such as the ureter or adjacent intestinal loops.^{29,119}

OTS endoscopic clips are designed to remain in situ long enough to allow defect healing but are traditionally left in place permanently. The duration of OTS endoscopic clip retention is variable (weeks to years) and unpredictable, dependent on the depth of tissue captured and native tissue response. OTS endoscopic clip removal is possible, if necessary, for endoscopic clip maldeployment or incomplete defect closure, to allow for additional lesion treatment or AE management. They also may need to be removed if there is adjacent neoplastic tissue that requires biopsy or resection.¹²⁰ Ovesco AG manufactures a bipolar device (remOVE system) for OTS endoscopic clip removal,

which is used to grasp and fracture the endoscopic clip by applying a direct electric current (DC) to the narrowest part of the endoscopic clip.¹¹⁹

Endoscopic clips are considered MRI conditional to 1.5 and 3 tesla (T), with the exception of the Olympus Quick-Clip2, which is MRI-unsafe. An animal study demonstrated physical deflection of the endoscopic clip under 1.5-T conditions, and 1 clip (Triclip; Cook Medical, Winston-Salem, NC, USA), which is no longer commercially available, demonstrated detachment from gastric tissue under experimental MRI magnetic field conditions.¹²¹ Radiology departments use standardized screening protocols for decisions regarding MR imaging in patients with previously placed endoscopic clips.

Endoscopic suturing (OTSS and TTSS)

The overall rate of AEs from OTSS leak and fistula closure are low, although it should be noted that most of these studies are published from expert centers with a high volume of endoscopic suturing procedures. Reported AEs related to OTSS include perforation and bleeding. When including OTSS for endoscopic sleeve gastropasty, AE rates between 2% and 5.2% have been noted, which includes intra- and postprocedural bleeding, leak, and pneumoperitoneum.¹²² One report of a gastric perforation from endoscopic sleeve gastropasty was presented, which required surgical exploration and repair.¹²³ The MAUDE database notes several cases of gastric and esophageal perforation from device manipulation, as well as inadvertent puncture of adjacent organs, pneumothorax, and gastrotomy. The details of these events are limited but may be more common with less experienced operators.

Likewise, the serious AE rate from TTSS appears to be low. An initial retrospective analysis totaling 93 patients across 8 centers reported infrequent adverse events in 2 patients (2.2%) during a mean follow-up of 34 days.⁴¹ One patient experienced right lower quadrant pain after a post-EMR colon defect closure. A second experienced bleeding at the site of an ESD closure requiring additional endoscopic therapy. A recent systematic review and meta-analysis included 12 studies with a total of 512 patients who underwent treatment for gastrointestinal fistula using TTSS. The overall adverse event rate was 7.3% (3.1%-11.5%, $I^2 = 81.6\%$), with the most frequent adverse event reported as pain (3.4%). Perforation was noted in 1.1% of cases (0.2%-2.0%, $I^2 = 0\%$).¹¹³ Another recent systematic review included 8 studies and 449 patients. The indication for TTSS was ESD or EMR defect closure. The adverse event rate was reported at 5.4% (95% CI, 2.7%-10.3%).¹¹⁶

Tissue sealants (CYA glue, fibrin sealant, and CSOs)

In a large, systematic review totaling 203 patients, 3 AEs related to tissues sealants that were graded as minor.⁸⁰ Theoretical risks of embolization are possible if the CYA

glue is inadvertently injected into a vessel, as is also noted from gastric variceal obliteration.⁴⁵

The primary adverse event reported with the use of CSOs is device migration. In the largest systematic review, there were 5 adverse events reported in 22 patients. Of these, 3 were device migration alone, 1 was fistula enlargement, and 1 included both fistula enlargement and device migration.⁴⁷

FINANCIAL CONSIDERATIONS

Given the expanding armamentarium of closure devices available to the endoscopist, it is important to consider cost when using various endoscopic closure devices. The cost of 1 TTS endoscopic clip ranges from \$150 (U.S.) to more than \$250, which would total more than \$1500 to \$6000 per closure when it comes to larger defects, such as those seen following EMR/ESD. The cost of the OTS endoscopic clip ranges from \$438 to more than \$600, with an additional cost for grasping and anchoring tools. The cost of Overstitch is in part volume based but has been reported to cost approximately \$700 to 1000 depending on the size of the hospital, with an additional cost of \$125 per unit for each suture and cinch. In contrast, 1 X-tack device along with a cinch can cost up to \$695. Determining best practice and cost-effectiveness of these various closure devices is desirable.

Cost considerations related to these devices include both the cost of the device and payer reimbursement for the procedure. Tables 1 and 2 provide cost estimates of endoscopic clips. It is important to note that costs vary widely between institutions depending on existing contracts and discounts. Tissue sealants vary in retail price. Various cyanoacrylate preparations are available but average roughly \$25/ampule. Fibrin sealant is more expensive and retails for approximately \$695. The Amplatzer CSO is significantly more expensive at approximately \$1000 to \$3000 depending on the size. There are no *Current Procedural Terminology (CPT)* codes dedicated for endoscopic closure of fistula, and hence these procedures need to be billed with either standard endoscopy codes (with fluoroscopy when indicated) or unlisted codes with supporting documentation.

TRAINING

TTS endoscopic clip placement is a basic technique that trainees acquire during GI fellowship. Individuals acquiring skills in endoscopic clip placement are expected to have achieved competency in routine upper endoscopy and colonoscopy. There are no established minimal numbers or other assessment criteria needed for credentialing following GI training in the United States. Placement of OTS endoscopic clips is not part of the core skill set acquired during GI fellowship. Competency can be achieved after a limited number of such procedures, although it is also largely dependent on the endoscopist's inherent skill set, which varies widely.

OTSS requires focused training and is typically not included in standard GI fellowship training. Few studies have assessed the learning curve of OTSS as it relates to defect closure; however, studies evaluating OTSS performance within an endoscopic sleeve gastropasty curriculum suggest a learning rate of 7 cases to reach 90% potential efficacy.¹²⁴ Although published data are lacking, successful use of OTSS relies on both a cognitive understanding of different suturing methods (ie, figure of 8, running, purse string, etc) and the technical aspects required to operate the device. In general, stent fixation may require the least amount of training given the relative simplicity and short distance needed to reach the esophagus. The use of OTSS in the duodenum and proximal colon is the most technically challenging.

TTSS has a perceived rapid learning curve since the catheter functions through the scope and is rather intuitive. In the initial, multicenter experience described by Mahmoud et al,⁴¹ endoscopic procedures were successfully carried out by endoscopists who were newly introduced to the device and received virtual or hands-on ex vivo training for up to 1 hour before their first clinical case. Unlike traditional OTSS, the skill level needed is not dependent on anatomical location. Accordingly, the technology will likely disseminate broadly in the endoscopy community. The ASGE offers several video- and course-based training programs to educate endoscopists on many of these devices, including defect closure using various endoscopic clips, OTSS, and TTSS.¹²⁵

AREAS OF FUTURE DEVELOPMENT

Over the past decade, the tools available to close complex defects of the GI tract have greatly increased. A variety of dedicated endoscopic clip advancements have been introduced, and suturing platforms are now widely available. Many of these tools have demonstrated significant efficacy for closure of mucosal and full-thickness defects, especially those that are acute, such as iatrogenic perforations. The ideal endoscopic treatment for chronic leaks and fistulas remains to be determined. Reliable full-thickness endoluminal closure in all areas of the GI tract is the ideal, as OTS endoscopic clips and suturing devices are not compatible with current enteroscopes for deep small-bowel pathology. Prospective randomized studies to determine the optimal closure methods are also lacking and would help inform practitioners on a data-driven algorithmic approach to mucosal defect closure.

CONCLUSIONS

An expanding array of new technologies has allowed greater ability to perform minimally invasive endoscopic closure of GI defects. Although TTS endoscopic clipping

was first developed as a tool for hemostasis, the market for larger-diameter and specialty endoscopic clips has facilitated reliable approximation of mucosectomy defects and small perforations. OTS endoscopic clips and suturing platforms provide an opportunity for full-thickness apposition with proven high success rates in closing larger perforations and selective leaks and fistulas. Suturing platforms are more complex than endoscopic clips and require additional training to achieve expertise. Newer TTSS systems provide a simpler approach but are likely less effective when full-thickness closure is needed. Chemical barriers and occluder devices offer additional options for challenging fistulas and leaks. Interventional endoscopy for the treatment of post-surgical leaks is often effective but may require multimodal therapy and multiple procedures. More studies are needed evaluating the best application and effectiveness of each technique, including on post-EMR/ESD adverse events, which remain a clinical challenge. Future studies should also assess training benchmarks, such as the percentage of patients requiring repeat endoscopy or surgical conversion for closure.

DISCLOSURES

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EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; FDA, Food and Drug Administration; GI, gastrointestinal; NOTES, natural orifice transluminal surgery; OTS, over-the-scope; OTSS, over-the-scope suturing; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy; PGA, polyglycolic acid; POEM, peroral endoscopic myotomy; RYGB, Roux-en-Y gastric bypass; SEMS, self-expandable metal stent; TTS, through-the-scope; TTSS, through-the-scope suturing.



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Current affiliations: Department of Gastroenterology and Hepatology, Weill Cornell Medicine, New York, New York, USA (1), Division of Gastroenterology, Duke University Health System, Raleigh, North Carolina, USA (2), Division of Gastroenterology, Department of Internal Medicine, Harvard Medical School and Massachusetts General Hospital, Boston, Massachusetts, USA (3), Department of Gastroenterology, Hepatology & Nutrition, Cleveland Clinic, Cleveland, Ohio, USA (4), Gastroenterology Services, Northwell Health Gastroenterology Institute, Zucker School of Medicine at Hofstra/Northwell Manhasset, New York, New York, USA (5), Division of Gastroenterology and Hepatology, University of Virginia Health Systems, Charlottesville, Virginia, USA (6), Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, USA (7), Department of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, Arizona, USA (8), Division of Gastroenterology & Hepatology, NYU Langone Health System, New York, New York, USA (9), Division of Gastroenterology and Hepatology, University of Tennessee Health Sciences Center, Memphis, Tennessee, USA (10), Center for Digestive Health, Penn Medicine Princeton Health, Plainsboro, New Jersey, USA (11), Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, Minneapolis, Minnesota, USA (12), Rutgers University School of Medicine, RWJ Barnabas Health, New Brunswick, New Jersey, USA (13), Division of Gastroenterology, Maimonides Medical Center, Brooklyn, New York, USA (14), Division of Gastroenterology, Boston Medical Center, Boston University School of Medicine, Boston, Massachusetts, USA (15).

Corresponding author: Mark Hanscom, MD, Department of Gastroenterology and Hepatology, Weill Cornell Medicine, New York, New York, USA. E-mail: bymarkhanscom@gmail.com.

Abbreviation: AEs, Adverse events; CO₂, Carbon dioxide; CPT, Current Procedural Terminology; CSOs, Cardiac septal occluders; CYA, cyanoacrylate; DAT, Dual Action Tissue; DC, direct electric current;