JGH Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.16722

REVIEW ARTICLE

Closure methods for large defects after gastrointestinal endoscopic submucosal dissection

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Key words

closure techniques, endoscopic closure, endoscopic submucosal dissection, endoscopic suturing, gastrointestinal lesions.

Accepted for publication 5 August 2024.

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Declaration of conflict of interest: The authors declare no conflicts of interest for this article.

Author contribution: Conception and design: R. G. and X. S.; provision of materials or patients: P. L. and X. S.; literature search and selection: R. G. and S. W.; drafting of the article: R. G.; and critical revision of the article: J. S., Z. H., S. Z., and X. S. All authors contributed to the article and approved the submitted version.

Financial support: This work was supported by the National Key R&D Program of China (grant number 2021YFC2400100) and Beijing Municipal Commission of Science and Technology (grant number Z191100006619082).

Abstract

Nowadays, endoscopic submucosal dissection (ESD) is commonly performed for the removal of large gastrointestinal lesions. Endoscopic mucosal defect closure after ESD is vital to avoid adverse events. In recent years, many innovative instruments have emerged and proved to be beneficial. In this paper, we conducted a thorough literature review and summarized the closure methods for large-size post-ESD mucosal defects over decades. We separated these methods into five categories based on the operational principle: "side closure" method, "ring closure" method, "layered closure" method, "hand suturing closure" method, and "specially designed device closure" method. Side closure with clips assisted by instruments such as threads or loops is applicable for each segment of the gastrointestinal tract to prevent postoperative bleeding. If the defect tension is too large to close with the traditional side closure methods, zigzag closure and ring closure could be applied to gather the bilateral defect edges together and achieve continuous closure. In the stomach and rectum with a high risk of submucosal dead space between the submucosa and muscular layers, side closure methods with muscle layer grasping clip or layered closure methods could enable the involvement of the deep submucosa and muscle layers. The ring closure method and specially designed devices including over-the-scope clip, Overstitch, and X-tack could resolve perforation effectively. Individual closure method requires endoscope reinsertion or sophisticated operation, which may be limited by the deep location and the narrow lumen, respectively. Although specially designed devices are expected to offer promising prospectives, the cost-effectiveness remains to be a problem.

Introduction

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are two commonly utilized endoscopic surgical procedures for gastrointestinal (GI) lesions. Generally speaking, ESD is superior to EMR because of the higher *en bloc* and curative resection rates for large lesions. However, greater difficulties and risks exist in such cases. Post-procedural bleeding and perforation are among the most serious major adverse events (AEs) following ESD. It has been reported that the rates of post-ESD bleeding and perforation in gastric lesions were 5–10% and $<3\%$, respectively, and in colorectal lesions, they were 2.7% and 5.2%, respectively.[1] Antithrombotic drug usage and large resected specimen size are the most significant factors that are associated with an increased incidence of post-ESD bleeding.[2–4] Specific lesion location, large lesion size, and muscle injury may be correlated with the occurrence of post-ESD perforation.[5] Therefore, efficient management preventing serious AEs is crucially required.

Prophylactic closure has been found to play an important role in the prevention of postoperative AEs, including delayed bleeding and delayed perforation, and in speeding up the defect healing process.[6,7] Through-the-scope clips (TTSCs) are the most traditional and widely adopted devices for defect closure after endoscopic resection. However, the clinical feasibility of TTSCs for adequate defect closure may be limited to wounds smaller than

2 cm due to the available wingspan and low clamping force. Therefore, many innovative instruments have been developed and proved to be beneficial in recent years. These include modified clip closure methods, techniques with the aid of other instruments such as threads or loops, and devices originating from surgical suture strategies. In addition, submucosal dead space (SDS) is an easily overlooked issue that tends to happen at thick sections such as the stomach and rectum using mucosa-to-mucosa closure, resulting in wound dehiscence after a few days.[8] Therefore, it is crucial to pick the appropriate closure method for the special cases.

In this paper, we conducted a thorough literature review and summarized the closure methods of large-size post-ESD mucosal defects over decades.

Literature review

A systematic review was performed using PubMed, Web of Science, Embase, and Cochrane for literature up to November 30, 2023, on endoscopic closure for large post-ESD mucosal defects. Two authors screened the literature independently. The strategy used to search in the database was based on the combination of subject words and free words, including endoscopic submucosal dissection, ESD, endoscopic resection, and closure. Relative articles were also considered. The exclusion criteria were (i) non-English studies, (ii) non-ESD procedures, and (iii) non-mucosal defects.

We divided the methods reported in the obtained literature into several categories according to the operation principle: "side closure" method, "ring closure" method, "layered closure" method, "hand suturing closure" method, and "specially designed device closure" method (Table 1).

"Side closure" method. The most limiting and difficult step for large mucosal defect closure is how to clamp the two farthest points of defect edges together, which is the reason why closure by normal TTSCs with restricted opening width is challenging. Therefore, a vital bridge connected to the two distal sides of the defect to serve as an anchor is required. Based on this, novel technologies have been constantly invented and modified these years. We categorize the "side closure" methods into three subgroups: side closure without muscle layer grasping clip, side closure with muscle layer grasping clip, and side closure in a tension-free zigzag way according to the different working principles and applicable scenarios.

Side closure without muscle layer grasping clip. The most common methods are based on a combination of clips and a certain instrument. A device called "loop clip" was firstly designed in 2008, which consisted of a nylon string loop pre-attached to a metallic clip.[9] After the loop clip was fixed at the mid of the distal side, a normal TTSC was then inserted to pull the loop clip and the grasped mucosal edge towards the proximal side and fixed at the mid of it (Fig. 1). This method is functionally similar to the later modified methods including clip closure with rubber band,[10] with three interconnected elastic silicone bands,[11] with elastic-rubber ring,[12] and with loop string.[13] The endoscopic sliding closure method was reported in 2015, which achieved closure of two opposite post-ESD defect sides by three clips and a ring-shaped thread.[14] Two clips grasped the thread and anchored on the two widest points of two sides. And the third clip hooked the thread and was drawn across to the defect edge, enabling the two sides to meet together. The line-assisted complete closure method was performed by Kato *et al*. in 2016.[15] A line was tied to an arm of a clip and fixed on the normal mucosa close to the defect margin. Then another clip was attached on the contralateral side. By tightening the line gently, the clips were gathered to reduce the defect size and facilitate the complete closure (Fig. 2). Procedure access rate of this method was 91% in 11 patients with defects after colorectal ESD (median size, 36 mm).[16] Similarly, slipknot clip suturing method,[17] string clip suturing method,[18] and thread-assisted closure method with locking clip[19] also achieved approximation of two sides making use of the tension of a string, thread, or dental floss. In the string-with-knotter suture method, the device was further improved to accomplish approximating the defect, tying the string, and cutting the excess string automatically.[20] Similarly, "loop 9" was invented and proved to be feasible and safe in 20 patients,[21] in which a slipknot and a felt pledget grabbed by the biopsy forceps worked as an anchor to tighten up the 9-shaped loop made with absorbable surgical suture. Recent novel techniques including nylon loops combined with the titanium clip closure method[22] and the "mucosal adaptive ring to close an endoscopic artificial ulcer" procedure[23] were developed, which were functionally similar but less cumbersome compared with the previous procedure. And the difference was in the anchor instruments.

The methods described earlier were effective in clinical practice but required complex accessories. In 2012, Otake *et al*. devised a closure method using small incisions.[24] To prevent the mucosa slipping, small incisions were artificially made around the defect during ESD, which enabled the clips to better grip and bring the edges closer. With this technique, it was reported in a study that 72 colorectal post-ESD large defects (34.3 ± 10.2 mm) were successfully closed with a mean time of 11 min.[25] A repositionable clip with strong jaws was reported in the hold-and-drag method[26] whose principle resembled the small-incision technique but with easier operation. The repositionable clip was utilized to hold one side of the mucosal defect, drag it towards the opposite side, and reopen and reclose the clip to keep both sides attached together. Recently, a novel reopenable clip designed with anchor prongs was a modified version of the repositionable clip, and it was adopted to close a defect measured 105 × 65 mm after ESD using the aforementioned method in the sigmoid colon.[27] In the clip-on-clip method, a clip was placed over another clip fixed slightly away from one side of the defect. The gap between the two clips served as an anchor, and the jaws of a third clip passed through the gap and pulled towards the contralateral side to reduce the defect area.[28] Nomura *et al*. applied this simple method to close 32 mucosal defects (median size, 34 mm) after colorectal ESD with a success rate of 97%.[29] Through-the-scope twin clip (TTS-TC) was firstly reported by Zhang *et al*. in 2019 and was used to successfully close a large gastric post-ESD defect (34 × 33 mm) in a live pig model.[30] TTS-TC was composed of a fixed column in the middle and two reopenable arms on both sides. The operation of two handles marked as different colors opened and closed the two arms independently, which enabled the TTS-TC to grasp two different tissues in turn and approximate the gaps of large defects. Previous study demonstrated the safety of TTS-TC for low delayed bleeding and high complete closure rate (0.94% and

Table 1 Summary of the closure methods for large-size post-ESD mucosal defects

Categories	Technique	Detail	Auxiliary instruments	Application segment	Scope reinsertion
Side closure (without muscle layer grasping clip)	Loop clip Clip-band closure Novel clip-band traction device Closure method with an elastic-rubber ring Loop string-assisted clip closure	A clip connected with a loop-like auxiliary instrument (with elastic contraction force or not) was fixed on one defect side, and another clip hooked and pulled the auxiliary instrument towards another side.	A loop of nylon string Rubber band Three interconnected elastic silicone bands Elastic-rubber ring 5-mm loop string	All segments	No
	Endoscopic sliding closure	A ring-shaped thread was clipped at the two points across the maximal diameter, and a third clip grasped one side of the ring thread across to a distant point from the edge of the defect.	Ring-shaped surgical thread	All segments	No
	Line-assisted complete closure Slipknot clip suturing method String clip suturing method Thread-assisted closure method using a locking-clip technique	A clip connected with a line (with the aid of tying, slipknot, or locking clip) was fixed on one defect side, and another clip hooked the line and was fixed on another side. Two distal defect edges were pulled together by tightening the line.	Nylon line Slipknot string (braided polyester) String (braided polyester) Dental floss	All segments	No
	Loop 9 Nylon loops combined with titanium clips Mucosal adaptive ring to close an endoscopic artificial ulcer	A loop or loop-like line was anchored by clips on the defect edges, and a special device that served as an anchor was used to tighten the loop strongly.	Absorbable monofilament with slipknot, felt pledget Nylon loop Barbed suture, loops	All segments	No
	Small mucosal incisions	Small incisions were artificially made around the defect and enabled the clips to better grip and pull the edges closer.	None	All segments	No
	Hold-and-drag closure technique	A repositionable clip was used to hold one side of the defect and drag it towards another side, and the clip was reopened and reclosed to keep both sides attached together.	Repositionable clip	All segments	No
	Novel reopenable clip	A novel reopenable clip with strong anchor prongs hooked and pulled one defect side to another.	Novel reopenable clip	All segments	No
	Clip-on-clip closure method	A clip was placed over another clip fixed on one defect side. The gap between the two clips served as an anchor, and the jaws of a third clip passed through the gap and pulled towards another side.	None	All segments	No
	Through-the-scope twin clip	Two arms grasp two different tissues in turn independently and approximate the gaps of large defects.	Through-the-scope twin clip	All segments	No
	Underwater closure	Water infusion could reduce the defect size.	Water	All segments	No

(Continues)

Categories	Technique	Detail	Auxiliary instruments	Application segment	Scope reinsertion
Side closure (with muscle layer grasping clip)	Reopenable-clip over-the-line method	Three clips with a line were fixed on the bilateral defect edges and the muscle layer. Two distal defect edges were pulled together by tightening the line.	Artificially modified clip, reopenable clip, nylon thread	More applicable for thick-walled segments such as the stomach and rectum	No
	Clip with line pulley securing		Dental floss		
	Accordion fold method		Reopenable clip, nylon line		
	O-ring closure	A loop anchored by three clips was fixed on bilateral defect edges and the muscle layer and pulled into the cap of the endoscopic variceal ligation device. An O-ring was fired around the clips to close the defect.	Nylon loop, endoscopic variceal ligation device, O-ring	More applicable for thick-walled segments such as the stomach and rectum	Yes
Side closure (in a tension-free zigzag way)	Barbed string	Clips were fixed on bilateral defect edges alternately in a zigzag way along the barbed string with tight stretching or dual thread with multiple rings.	Barbed string	More applicable for large-tension defects of all segments	No
	Elastic thread delivery hood		Dual-traction hood device		
Ring closure	Endoscopic purse-string suture method	An endoloop was fixed along the margin of the defect by clips. By tightening the endoloop, the defect edges were gathered.	Double-channel endoscope, endoloop	All segments	No
	Pre-detached loop and clip method		Endoloop		
	Bead, loop, and clip closure		Endoloop, bead		
Layered closure	Double-layered suturing Modified double-layered suturing	Clips were placed on the submucosal or muscle layer center to shrink and fold the defect.	None	More applicable for thick-walled segments such as the stomach and rectum	No
	Mucosa–submucosal clip closure	Each arm of the clips hooked both the mucosa and the submucosa of the defect edge to bring the edges closer.	None	More applicable for thick-walled segments such as the stomach and rectum	No
Hand suturing closure	Endoscopic hand suturing	Absorbable barbed suture and needle were performed like surgical suturing.	Barbed suture, needle, biopsy forceps, or needle holder	Not applicable for narrow-lumen segments such as the duodenum and colon	Yes
Specially designed device closure	OTSC	A special clip with several prongs was released to close the defect with the aid of twin grasper forceps or anchor forceps.	Specially designed device	All segments	Yes
	Overstitch	Running stitches with a needle sutured the defect in a continuous or separate pattern.	Specially designed device	Not applicable for narrow-lumen segments such as the duodenum and colon	Yes
	X-tack	Four individual helical coil tissue tacks preloaded on a single polypropylene suture were released to close the defect.	Specially designed device	All segments	No

ESD, endoscopic submucosal dissection; OTSC, over-the-scope clip.

96.3%, respectively) in colorectal lesions with a median size of 40 mm, even including patients on anticoagulants.[31] A recent study reported the application of TTS-TC for 13 large mucosal defects up to 85 mm after ESD in porcine stomachs with 100% closure rate, although with a partial wound dehiscence rate of 38.5% 1 week later.[32] Also, TTS-TC was also used to successfully

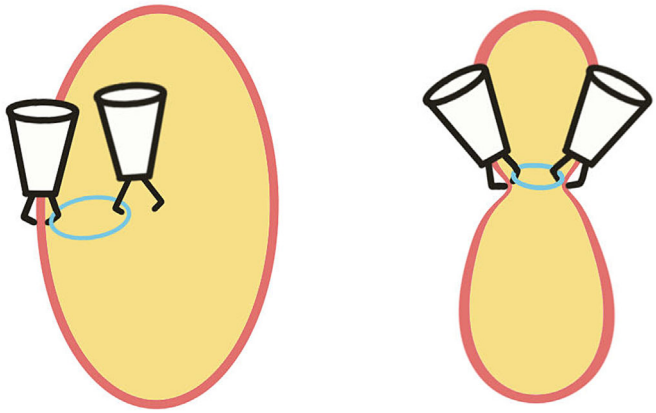

Figure 1 Illustration of the "side closure" method with loop: After a loop is fixed on one side of the defect by a clip, another clip grasps and pulls the loop towards the opposite side.

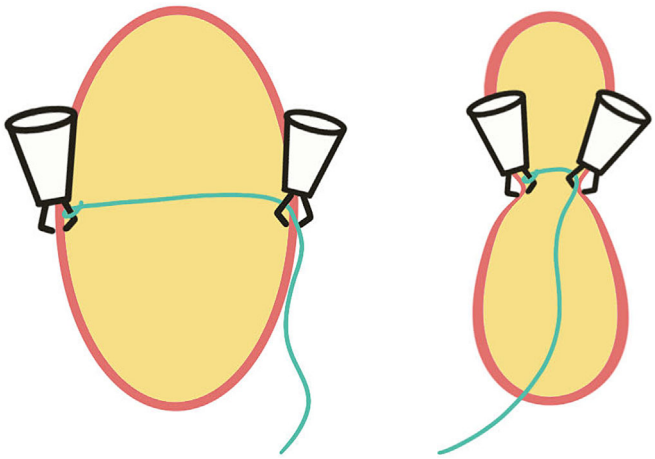

Figure 2 Illustration of the "side closure" method with line: Two clips are attached on both sides of the defect with a line passing through them, and the clips were gathered by tightening the line.

close large perforation after endoscopic full-thickness resection (EFTR) with its powerful clamping ability and flexible maneuverability.[33] Therefore, TTS-TC is a highly promising novel device for large endoscopic defect closure, and further studies should be conducted to confirm its clinic value.

It has been reported that the resection defect size presented a significant reduction after water infusion during EMR, which facilitated the following complete clip closure.[34] In 2018, underwater clip closure was used to successfully close all the 21 large defects (median size, 31 mm) after colorectal ESD without any delayed AEs.[35] Because of the efficient and easy performance and significant advantage of decreasing post-ESD electrocoagulation syndrome, underwater clip closure has been increasingly used for intermediate and large lesions in the GI tract.[36]

Side closure with muscle layer grasping clip. In thick-walled GI segments such as the stomach and rectum, conventional mucosa-to-mucosa side closure has a high risk of SDS between the submucosa and muscular layers. Therefore, side closure methods with muscle layer grasping clip are developed to enable the involvement of the deep submucosa and muscle layers. In 2021, Nomura *et al.* described the reopenable-clip over-the-line method (ROLM).[37] After ESD, reopenable clips with a line were attached to the bilateral edges of the mucosal defect and muscle layer, which allowed no dead space between the mucosa and muscle layers. ROLM had been performed on 50 patients with large gastric mucosal defects (median size, 45 mm)[38] and 30 patients with colorectal ones (median size, 45 × 39 mm)[39] following ESD and proved to be a feasible strategy. The later "accordion fold" method[40] is similar to the ROLM in the principle of operation. Further, endoscopic ligation with an upgraded device of O-ring closure (E-LOC) was developed[41] and became widespread in several difficult defect closure cases.[42,43] A surgical nylon loop was placed around the defect edge, and three clips were attached on both margin sides and the exposed muscle layer to anchor the loop. Thereafter, a variceal ligation device was used to pull and house the loop tail grasped by a clip applicator into the cap. Finally, an O-ring was released around the clips to close and tighten the defect strongly. This procedure was repeated at the interrupted location of the defect to achieve complete closure. A prospective study reported the application of E-LOC for closing defects (31.6 ± 13.5 mm) after gastric ESD in 48 patients who were taking antithrombotic agents.[44] The post-operation bleeding rate and complete closure rate were 0% and 97.9%, respectively, and no AE was observed. Recently, a method named clip with line pulley securing (CLiPS) technique was demonstrated by Parekh *et al.*,[45] wherein in place of the O-ring, the device to approximate the edges is a pulley system made of a modified anchoring clip. It was formed by cutting the distal jaws off a large-caliber

reopenable clip and passing through the line at the base of it, which made the line independent of the endoscope giving free maneuverability.

Side closure in a tension-free zigzag way. Zigzag closure is a special subgroup of the side closure method, which means closing defects by continuous alternating fixation of the bilateral edges. Recently, the method of clips combined with absorbable barbed string for defect closure was developed. Clips were anchored on the bilateral edges of the defect alternately along the barbed string, whose barbs enabled tight stretching and avoided endoscopic knotting. This method was first used in a gastric case, wherein the tension of the tissue was too large to clip together in the traditional way.[46] A recent study indicated its feasibility in 31 patients with large defects (median size, 34 mm) after colorectal ESD or EMR with a complete closure rate of 93.5%.[47] The elastic thread delivery hood was designed with a dual thread consisting of multiple rings stored in thin side pockets of the hood.[48] During defect closure, the first ring was grasped by a clip and attached to the defect edge. Then the thread was released when pulling back the endoscope. And the second ring was grasped by the second clip and fixed on the opposite defect edge. The defect was approximated with the traction of the thread. By repeating the earlier procedure, the defect could be closed completely (Fig. 3). This novel device is a relatively convenient method with no limited to lumen space and defect size and has been used successfully for closure in large colonic and rectal post-ESD defect.[49]

"Ring closure" method. In "side closure" methods earlier, the defects were closed in an interrupted pattern, which had a potential of incomplete closure and increased the risk of defect dehiscence. In 2014, Zhang *et al*. reported a novel technique named the endoscopic purse-string suture (EPSS) method for closure of gastric defects after EFTR and perforations due to ESD.[50] In this technique, an endoloop, several metallic clips, and a double-channel endoscope were required. First, the endoloop was fixed along the margin of the defect by several anchored clips. By tightening and fastening the endoloop, the edges of the defect were gathered, and the defect was completely closed (Fig. 4). However, performance with double-channel scope is relatively technically difficult and cumbersome. In 2015, a modified method using a pre-detached loop and clips with a single-channel gastroscope was developed.[51] To achieve all steps of the closure via a single working channel, the endoloop was pre-detached on a clip, inserted and fixed on the post-ESD defect margin, followed by being pulled and tightened by a hook device to close the defect. A study demonstrated that the pre-detached endoloop system was successfully applied to close 18 proximal colonic defects (mean size, 28 mm) after ESD, and no related AEs were recorded.[52] Afterwards, the device of EPSS was further improved. A clip-fixed endoloop included a tip of an endoloop threaded to a clip's tooth and enabled the endoloop to hide in the outer sheath of the clip and be opened properly by moving the outer slider.[53] And a modified hook device with a shape of "J" to easily grasp the endoloop tail was invented.[54] In 2018, Wu *et al*. proposed endoscopic prepurse-string suture (P-EPSS) method for gastric wall defect after EFTR to decrease the difficulty in manipulation and turn passive perforation to active perforation.[55] The difference between EPSS and P-EPSS was that the endoloop and clips were anchored the defect in advance, which allowed the immediate closure by tightening the endoloop when the tumor was finally resected in P-EPSS. P-EPSS is more suitable for situations where the lesions originating from the deep mucosa are more prone to perforations. A recent study concluded that P-EPSS could shorten the closure time and achieve secure complete closure after endoscopic resection including ESD and EFTR.[56] "Bead, loop, and clips closure" method[57] reported recently also belonged to the "ring closure" methods but was modified in equipment to reduce the difficulty grasping the endoloop tail.

"Layered closure" method. In 2012, an endoscopic double-layered suturing method was introduced for closing large mucosal defects after EMR or ESD.[58] In this method, clips were placed on the submucosal layer center to shrink and fold the

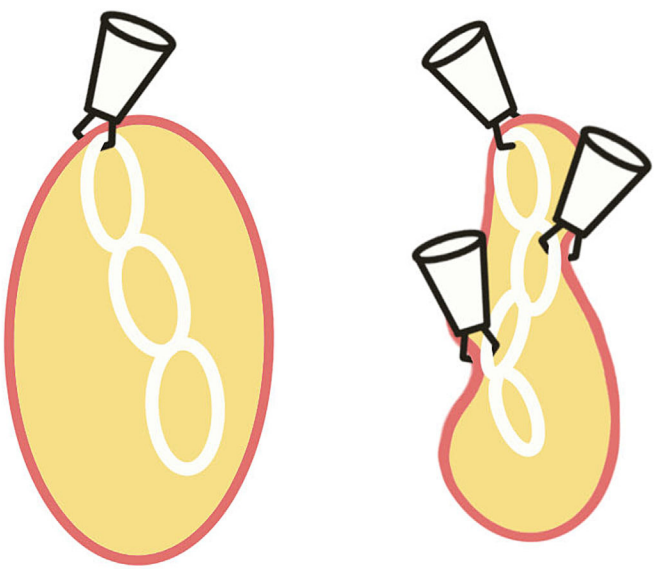

Figure 3 Illustration of the "side closure" method in a tension-free zigzag way with an elastic thread delivery hood: The thread rings are anchored on the bilateral edges of the defect alternately by clips.

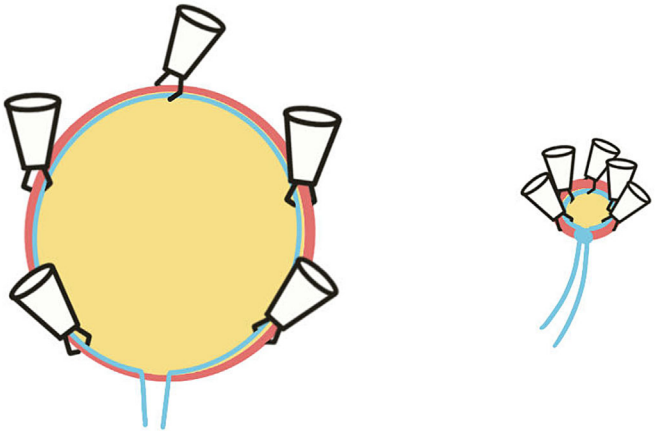

Figure 4 Illustration of the "ring closure" method: The edges of the defect are gathered by tightening and fastening the endoloop fixed around the defect.

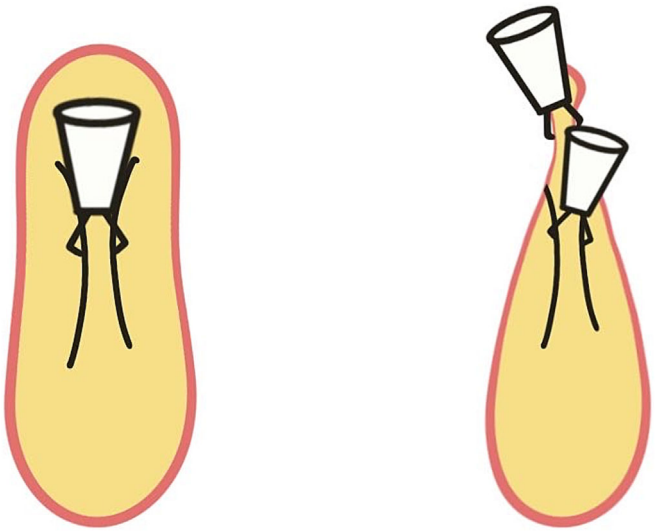

Figure 5 Illustration of the "layered closure" method: Clips are placed on the submucosal layer center to shrink and fold the defect, followed by additional clips added onto the mucosal layer.

defect. Then, additional clips were added to the mucosal layer between the first set of clips (Fig. 5). However, this method has not been widely utilized. Later on, a modified double-layered suturing called the origami method (OGM) was attempted in 47 cases (38–85 mm) after colorectal ESD with a complete closure rate of 94% and no AE observed. In the OGM, the muscle layer is folded with TTSCs, making a few peaks like in an origami, followed by other TTSCs connecting the peaks and shrinking the defect in order to close both the mucosal and the muscle layer. OGM can achieve robust closure in cases with more than 50% circumferential mucosal defects, even for thick-walled rectal large defects.[8] Another approach making use of the tension generated by clamping clips on mucosa and submucosa to reduce the size of the defect is the mucosa–submucosal clip closure method reported in 2017.[59] Each arm of the clip hooked both mucosa and submucosa of the defect edge after ESD, which brought the two edges close to each other and enabled additional clips to grasp both sides. The method was successfully performed in 24 out of 25 patients with colorectal post-ESD defects (31.2 ± 11 mm).[60] However, this method may be unreliable for closure in patients who underwent gastric ESD due to the thick and hard gastric wall.[61]

"Hand suturing closure" method. Inspired by the surgical suturing method, non-size-limited endoscopic hand suturing (EHS) was developed by Goto *et al*. in 2014.[62] Mucosal defects after ESD were created in isolated stomachs of pigs. And an absorbable barbed suture with a needle was firmly grasped by a biopsy forceps or needle holder and used to perform a unidirectional and knotless suture endoscopically. It was shown that the closure strength was significantly greater in the EHS group compared with the loop closure group and clip closure group.The validity and effectiveness of EHS for defect closure after gastric ESD was confirmed in *in vivo* pigs and clinical patients in 2017.[63] Akimoto *et al*. reported that successful EHS for gastric post-ESD mucosal defect closure contributed to decrease the risk of delayed AEs such as bleeding and perforation by accessing the healing process both endoscopically and histologically *in vivo* porcine models.[64] In 2020, EHS was used for gastric post-ESD defect closure in 30 patients (36.0 ± 7.1 mm) who were taking antithrombotic drugs or not[65] and for colorectal post-ESD defect closure in 11 patients (median size, 38 mm).[66] It was found that EHS could implement completed and sustained closure for both gastric and colorectal wounds with favorable outcomes. However, the long procedure

time and the endoscopist's substantial experience with the technique led to the limitation of its widespread use in clinical practice.

"Specially designed device closure" method. The over-the-scope clip (OTSC) system is an endoscopic full-thickness suturing device that consists of a clip with several prongs installed on an application cap and a releasing mechanism including a hand wheel and a thread retriever. In addition, auxiliary forceps are necessary and comprise two types: twin grasper forceps and anchor forceps. The former operates similarly to the TTS-TC, in which two arms grasp both sides of the large defect, followed by the OTSC clamping. The latter is applicable to indurated tissue closure with three stretchable needles grasping it simultaneously.[67] OTSC was firstly reported by Kirschniak *et al.* in 2007 for complex bleeding, deep wall lesions, and perforations in the GI tract.[68] Now, it has been widespread worldwide for strong and sustained closure in large mucosal defects, perforations, fistulas, and anastomotic leakages due to its strong clamping force. Previous studies have indicated that the OTSC served as an effective strategy for closing large complex post-ESD mucosal defects in the stomach, duodenum, and colon with a high success rate and few AEs.[69–71]

Overstitch is a clinically frequently used suturing system that has been used in a wide range of applications including endoscopic mucosal defect, full-thickness defect closure, fistula repair, and stent fixation. It allows complete closure by running stitches with a needle in a continuous or separate suturing pattern. The overstitch suturing system was evaluated for the closure of large post-ESD defects and indicated to be fast, safe, and efficient.[72] The mean lesion size was 42.5 mm, and the mean suturing time was 10 min, and neither immediate nor delayed AEs occurred. However, a double-channel endoscope was required for Overstitch. Afterwards, a new generation of Overstitch Sx, compatible with a single-channel endoscope, was developed. A recent prospective study assessed the Overstitch Sx system as a safe and effective method in large defect closure after ESD (53.8 ± 25.2 mm) with a technical success and clinical success of 93.9% and 90.9%, respectively.[73]

X-tack received US Food and Drug Administration approval for clinical use in 2020 to achieve through-the-scope suture closure.[74] The device is composed of four individual helical coil tissue tacks preloaded on a single polypropylene suture. It could pass through a standard gastroscope or colonoscope with a minimum working channel diameter of 2.8 mm with no need to withdraw the device from the patient. The tacks were deployed serially adjacent to the mucosal defect with a common pattern of N/Z or figure-of-8/X. After all the tacks were released, the suture was cinched under the tensile force to close the defect. A retrospective multicenter study involved 93 patients and reported that technical success was achieved in 83 cases including large defect closure after ESD, EMR, fistula, and stent fixation.[75]

Discussion

To date, no consensus on the closure methods for endoscopic large defects has been reached. In this paper, we comprehensively reviewed the literature on global novel strategies for closing large mucosal defects after ESD. We separated these methods into several classes based on the operational principle, which are available in diverse clinical scenarios.

ESD has become the first-line treatment for lesions located in the GI tract. But there are distinctions in the structural characteristics of various segments of the GI tract. In thick-walled GI segments like the stomach and rectum, grasping only the mucosa may result in an SDS formation between the submucosa and the muscularis propria, which tends to cause wound dehiscence and postoperative bleeding.[8] Therefore, closing all layers of the defect is vital for achieving robust closure. Among the side closure methods, the accordion fold method, ROLM, CLiPS method, and O-ring closure are methods that meet the principle of grasping the muscle layer with clips. The layered closure method can achieve a more reliable closure to eliminate SDS. It can also be performed by hand suturing closure and specially designed device closure including OTSC, Overstitch, and X-tack, however with the limitation of technically demanding and high prices. In the thin-walled duodenum and colon, muscle injury and excessive electrocautery during hemostasis are common risk factors of delayed perforation. Closure of large mucosal defects in a completely continuous way in these segments results in an increasing risk of stricture in the future, in which a separate side closure method or suturing with Overstitch or barbed string is applicable. Further, it is also required that the closure device could fall off spontaneously and promptly to prevent the formation of ulcers and strictures. For novel closure methods, the reliability of closure durability and whether detaching spontaneously is questionable. It is difficult to undertake surveillance endoscopy repeatedly in a short time after operation to evaluate these characteristics because patients will suffer from extra financial burden and physiological pain. And more studies need to be designed to verify this.

In the recent study of TTS-TC,[32] it was found that longer operation time and repeated grasping of TTS-TC might worsen the mucosal edema, which was significantly related to the defect dehiscence. Therefore, the operation convenience of the devices should also be considered, which plays a highly important role in the closure time and closure quality. Several methods are effective but have multiple technical steps or require complex supplement. OTSC has been increasingly used in a wide range of situations, but it is necessary to remove the scope to mount it on the scope and reinsert the scope, which requires sufficient training and technical expertise of endoscopists. For example, if the lesion is located in the right-sided deep colon, a technique with no need of scope reinsertion is more appropriate. As to the lumen space, an anatomically narrow working space such as the esophageal and colorectal lumen also limits endoscopic manipulation. The expected methods like EHS and Overstitch need an adequate operative field to conduct, which greatly increases the difficulty of operation and reduces its viability.

Additionally, the issue of cost–benefit balance cannot be ignored. Facile devices composed of clips and threads may be relatively cheaper, but they need large sample randomized controlled trials (RCTs) to confirm their reliability. Specially designed devices with automation including OTSC, Overstitch, and X-tack are now being marketed and expected to offer promising prospectives, but their cost-effectiveness remains to be a problem.

In summary, despite the proliferation of novel effective closure methods for large mucosal post-ESD defects, more RCTs are

needed to further explore the best choice for populations with different risk factors and different clinical scenarios.

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