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**New devices and techniques for endoscopic closure of gastrointestinal perforations**

Li Y *et al*. Endoscopic closure of GI perforations

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**Abstract.**

Gastrointestinal perforations, as an emergency needs to be managed quickly, possess a high morbidity and mortality. Treatments that were applied to close the perforations for the patients are usually different due to various situations, from surgery to endoscopic therapy. Nowadays, with the development of new devices and techniques, endoscopic therapy is becoming more and more conventional and popular. However, there were different indications and clinical efficacy between different methods, because of the diversity and property of endoscopic devices and techniques. It also depends on several factors, like the precise localization of the perforation, the size of the perforation and the length of time between the occurrence and the diagnosis of the perforation. In this study, we performed a comprehensive review of various devices and introduce the different techniques that are considered effective for the treatment of gastrointestinal perforations. In addition, we focus on the different methods that were applied to make successful closure based on both the literature and our clinical experiences.

**Key words:**Gastrointestinal perforations; Devices; Techniques; Endoscopic closure; Treatment

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**Core tip:** We introduce and discussed endoscopic devices and techniques in this paper based on both the literature and our clinical experiences. Endoscopy doctors should avoid perforation consciously, especially during therapeutic procedure. Sometimes, intentional perforation is necessary for complete removal of tumor. However, the integrity of mucosa should be considered and the retained mucous membrane could contribute to the effective closure of the perforation after full-thickness resection. We hope to provide more information about choosing the appropriate method to close perforations effectively.

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**Introduction**

Gastrointestinal perforation is defined as the presence of gas or luminal contents outside the gastrointestinal tract. In recent years, gastrointestinal perforations with a high incidence have raised more and more attentions. The absolute number of perforations is likely to increase, because of the widespread implementation of endoscopic screening programs and the expansion of the indications for endoscopic therapy[[1](#_ENREF_1)]. Many reasons like iatrogenic factors, spontaneity, foreign body, trauma and surgery, *etc*. account for gastrointestinal perforations[[2-4](#_ENREF_2)]. Among these etiologies, iatrogenic factors contribute most to the increased incidence of perforations which includes endoscopic examination, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), peroral endoscopic myotomy (POEM), endoscopic retrograde cholangiopancreatography (ERCP), stricture dilation, foreign body removal and malignant tumors[[2](#_ENREF_2),[5-9](#_ENREF_5)]. The incidence of iatrogenic perforations varies in diagnostic and therapeutic endoscopy and ranges from 0.029% to 5%[[10](#_ENREF_10),[11](#_ENREF_11)]. With the developments of new devices and techniques, endoscopic closure has been considered as a primary method and should be an option of priority, compared to surgery or conservative treatments[[12-14](#_ENREF_12)]. Endoscopic closure has demonstrated its great advantages with high success rate, minimally invasion, short hospitalization and low medical expense. Based on the latest studies, endoscopic devices and techniques are considered to be a safe and effective measure to close gastrointestinal perforations[[15-27](#_ENREF_15)]. In our previous work, we firstly utilized multiple-band ligators to successfully repair a lateral duodenal ERCP-related perforation[[27](#_ENREF_27)]. The overall rate of successful endoscopic closure was about 89.9% with different devices and techniques get a success rate ranging from 87.5% to 100%[[4](#_ENREF_4)]. Many studies have described various kinds of endoscopic devices and techniques. However, it’s a pity that there is no systematic introduction about latest fast-changing devices and techniques. Recently, we have reported two kinds of new techniques for closure of perforation and made successful attempts. In this study, we introduced and summarized different endoscopic devices and techniques based on latest research and our previous experience. We hope to provide more suggestions for physicians to apply the appropriate method to close perforations effectively and improve the success rate of endoscopic closure.

**New devices and techniques**

***Endoclip techniques***

Clipping techniques for endoscopic closure of gastrointestinal perforations are the most common treatment methods[[11](#_ENREF_11),[28](#_ENREF_28),[29](#_ENREF_29)]. From treating gastrointestinal bleeding to perforations, endoscopic clips play an increasingly important role. Conventional endoscopic clips, which also can be named as through-the scope clips (TTSC) can effectively close the perforations of the esophagus, stomach, duodenum and colon[[5](#_ENREF_5),[6](#_ENREF_6),[9](#_ENREF_9),[19](#_ENREF_19),[30-32](#_ENREF_30)]. There was no failure in a total of three patients with esophageal perforations following endoscopic mucosal resection (EMR) reported by Shimizu *et al*[[5](#_ENREF_5)] managed by endoclips. Sekiguchi *et al*[33] had also reported complete endoscopic closures of gastric perforation[[34,35](#_ENREF_33)]. Attentions should be paid conservatively to those patients with a medical history of laparotomy, as there was a case failed[[33](#_ENREF_35)]. Yang *et al*[[36](#_ENREF_36)] demonstrated a success rate of 95.5% with effective clipping in colonoscopy-associated perforations. When the tissues around the edge of defect were inflamed or indurated, it may be difficult for endoclips to close the perforation.

The combination of the clips and other devices and techniques is common to close some special perforations. Tanaka *et al*[37] applied clips and a detachable snare to close a large esophageal perforation since it was difficult for clips only to manage[[37](#_ENREF_37),[38](#_ENREF_38)]. Using a 2- channel scope, clips were placed equably to fix the detachable snare around the defect. When the rubber stopper was tightened, the perforation was closed successfully[[38](#_ENREF_38)]. Endoloop and metallic clip interrupted suture was also used in closing gastric perforation. Shi *et al*[[39](#_ENREF_39)] proved that using endoloop and metallic clip interrupted suture to repair gastric defects resulting from endoscopic full thickness resection (EFTR) was safe, easy and feasible. The endoloop was anchored to both sides of the defect with two clips. After the maneuver was repeated enough around the defect, endoloop was tightened and then the defect was closed. It had been proved to be safe and quick with the only side effects of slight abdominal pain and fever in the early days.

Large mucosal defect areas usually occurred during endoscopic submucosal dissection (ESD). A new closure device, named loop clip was also designed to close large mucosal defect after ESD[[40](#_ENREF_40)]. The loop clip was anchored to the edge of the mucosal defect at the distal side, then a normal clip was inserted and attached at the proximal side, the nylon loop attached to the loop clip then had first been grasped. The first conventional endoscopic clip was placed beside the deployed loop clip to bring the distal edge to the proximal side. Next, the second clip was placed beside the loop clip on the opposite side of the first clip. Repeated this operation until the whole defect was closed.

***Over the scope clip system***

However, gastrointestinal perforations sometimes are difficult to be managed using endoclip techniques or the nylon loop. The over the scope clip system (OTSC) system can be more effective than TTSC in an emergency or complex situation. OTSC is more suitable for larger defects and more effective for closing a fistula. The principle of OTSC system to close defects is depending on its twin grasper. When graspers were released to grasp the sides of the lesion, they were retracted completely and the perforation was closed. The advantages of OTSC system could be seen in the case report by Ono *et al*[[8](#_ENREF_8)]. Using the OTSC system, they closed the esophageal perforation, as there was an esophageal stenosis. Though OTSC system has strong abilities to solve difficult cases, shortness appears as well. It’s hard to remove the clips once they are placed. And the grasper isn’t flexible to rotate. We usually applied OTSC system complex situation, such as the perforation is large or the perforation is difficult to manage by endoclips. Recently, we successfully close a large perforation during ESD. The submocosal tumor (SMT) was about 20mm and originated from the deep muscularis propria layer. In order to remove the tumor completely, we made full thickness resection and a large perforation occurred. Then OTSC and clips was applied to make successful closure (Figure 1). All of these new devices and techniques had a good efficacy on closing different large and complicated perforations. However, whether they can be used widely in the clinic treatment or not still need more clinical studies to make sure.

How to choice an appropriate clipping technique to cure the perforations? The normal endoclips are suggested to use when the perforation’s diameter is less than 10-20 mm. OTCS clips are suitable to close the perforation with the diameter less than 30mm or the edge of mucosal swelling and evaginating. The larger perforation can be closed effectively by the combination of the clips and other devices or techniques.

In a conclusion, compared to other endoscopic new devices and techniques, clipping techniques are much more common in closing perforations. It has been first choice for most situations to close the perforations instead of surgery or conservative treatment[[41](#_ENREF_41)].

***Self-expanding metal and plastic stent***

Recently, temporary stent placement has been another endoscopic treatment for patients with perforations. There are mainly two stents with different shapes, fully covered self-expanding metal/plastic stents (fSEMS/ fSEPS) and partially covered self-expanding metal stents (pSEMS)[[2](#_ENREF_2),[20](#_ENREF_20),[23](#_ENREF_23),[42](#_ENREF_42)]. Fully covered ones have the advantages of good drainage and closure of perforation sufficiently without obvious complications[[23](#_ENREF_23),[43](#_ENREF_43)]. Unfortunately, they all nearly have a high migration rate that delays the recovery[[43-45](#_ENREF_43)]. pSEMS have a very low migration and make up the defect of fully covered ones. Nevertheless, it is a great challenge to remove them because of the tissue embedding[[46](#_ENREF_46)]. Anyway, they provide more methods for patients to choose and in some situations play a much better function than other devices and techniques. And most of all we need use this new technique correctly. In view of both the literature and our clinical experiences, for esophageal perforation with stenosis, the defect’s diameter over than 20-30 mm and the presence of malignant lesions around the defect, stents are a good choice. Gastric perforation near the pylorus, perforation caused by dilating anastomotic stricture and perforation not near duodenal ampulla go for the stents treatments.

Kumbhari *et al*[[20](#_ENREF_20)] had reported that an iatrogenic pharyngoesophageal perforation was closed by fSEMS after three days. Only a little working space and risk of pulmonary aspiration made it almost impossible to apply endoscopic clips, OTSC or endoscopic suturing, *etc*. It highlighted the importance of stents instead. Ribeiro *et al*[[21](#_ENREF_21)] had used a combinational technique to close a large fistula with fibrin glue, partially covered stent and biological patch perfectly. Stents are much more effective on esophageal perforation for the 100% success rate in the technical aspect. Generally speaking, when stents were used in treatments for upper gastrointestinal perforations, anastomotic leaks and fistula, the success rate ranged from 65% to 88% with different migration rate[[23](#_ENREF_23)].

***Endoscopic band ligation***

As we know, endoscopic band ligation (EBL) is one of the first-line choices for the management of gastroesophageal varices and variceal hemorrhage in cirrhosis[[47](#_ENREF_47)]. EBL is also safe and effective when it is performed to treat dieulafoy lesion and diverticular bleeding[[48-50](#_ENREF_48)]. Furthermore, EBL is also considered to show promise as an effective and safe treatment for gastric small gastrointestinal stromal tumors[[51-53](#_ENREF_51)]. In the recent years, EBL is applied in the area of closing GI perforations, like gastric, duodenal, colon and rectal perforations. In most cases, EBL is an alternative choice to close those perforations after the metal clips failed. According to the studies worldwide, the perforation could be closed at a very high success rate when EBL was applied. EBL are easy, safe, time-saving and effective as well. Lee *et al*[[26](#_ENREF_26)] compared the endoscopic band ligation with endoclip for closure of colonic perforation. Closure by EBL cost much less time than closure by endoclipping (3.2 ± 1.7 min *vs* 6.8 ± 1.3 min, *p* < 0.01). We had ever reported a successful close of lateral duodenal perforation by endoscopic band ligation after endoscopic clipping failure[[27](#_ENREF_27)]. Because of the fragile edge of the tear, the metal clips failed. We first applied the EBL to close this iatrogenic perforation. Though the endoscopic management of a duodenal perforation is much more difficult than the others, the patient’s perforation was closed by EBL technique perfectly without any symptoms after six months. We revealed that EBL may be easier and faster than endoclipping, which could be considered as the primary repair of duodenal perforations[[27](#_ENREF_27)].

Han *et al*[[54](#_ENREF_54)] carried out a case study to evaluate the clinical efficacy and safety of EBL technique in the gastric perforations when endoclips closure failed. Successful closures were achieved in all cases. However, the number of patients is limited and this study was not comparative study. Han *et al*[[55](#_ENREF_55)] also had similar case studies in colon perforations and get the same results. Moon *et al*[[56](#_ENREF_56)] also used the EBL technique to close a rectal perforation caused endoscopic submucosal dissection (ESD), with reasonably good results as well.

There is no doubt that new devices and techniques have the defects. EBL may prolong the hospital stays by binding together more tissue than required. What’s more, it accounts for the injury to the adjacent organ[[25](#_ENREF_25),[26](#_ENREF_26), [54](#_ENREF_54)]. Much more studies and developments are needed to expand its clinical use.

***Biological glue***

Among the numerous tissue sealants, as a mixture of fibrinogen and thrombin, biological glue is widely used[[2](#_ENREF_2),[3](#_ENREF_3),[57](#_ENREF_57)]. Originally, the fibrin glue was used in the area of gastroduodenal ulcer bleeding, wound healing and bleeding caused by resections of the gastrointestinal tracts[[58](#_ENREF_58)]. Fibrin glue can form a clot in vivo and can be fully reabsorbed by our macrophages in nearly two weeks[[59](#_ENREF_59),[60](#_ENREF_60)]. The fibrin glue can promote the growth of proliferating cells and increase the number of microvessels[[61](#_ENREF_61)]. Besides, the expression of growth factors was also upregulated by fibrin glue, which all contribute to heal defects and bleedings[[61](#_ENREF_61),[62](#_ENREF_62)].

Many recent researches have verified the efficacy of biological glue to close the GI defects. Kotzampassi *et al*[[57](#_ENREF_57)] had gained a 96.8% success in a total of 63 patients with anastomotic leaks. Mutignani *et al*[[59](#_ENREF_59)] obtained similar results as for fibrin glue for treatment of GI perforations. The whole six patients in his study with refractory post-ERCP bleeding were treated with fibrin glue. The study revealed that fibrin glue may provide a new therapeutic choice to cure ERCP-related type 1 perforations after the clipping techniques failed[[59](#_ENREF_59)]. Biological glue is mainly applied to close fistula and leak. However, the application to close the GI perforations is scarce and deserves much more exploration.

In order to improve the efficacy of biological glue, Doyama *et al*[[63](#_ENREF_63)] adopted the treatment with the polyglycolic acid (PGA) sheets, fibrin glue, and clips. This new devices and techniques solved the problems of gravitational influence on PGA and the weakness of clips to close larger defects more than 30 mm in diameter[[32](#_ENREF_32)]. Although biological fibrin seemed inspiring and easy to apply, the disadvantages should get more attentions. It is unknown whether biological fibrin is suitable for retroperitoneal perforations and how to handle the emergency about fibrin clot infection. What’s more, frequent use of fibrin glue may increase the surgery difficulties[[59](#_ENREF_59),[60](#_ENREF_60)].

***Innovative*** ***new*** ***endoscopic devices for suturing***

At present, there are a number of innovative new endoscopic devices for suturing. What is used mostly is still the Bard EndoCinch suturing device (Davol, Cranston, RI)[[64](#_ENREF_64)]. But most of the suturing devices developed in last two decades are cumbersome and expensive. More and more physicians now are searching for simple but useful suturing devices[[65](#_ENREF_65)].

Bergstrom *et al*[[65](#_ENREF_65)] had ever conducted a clinical study with a new simple stitching technique. Relied on two threads in the tissue on each side of a defect, then the stitching technique locked the threads and finally the defect was closed perfectly[[65-67](#_ENREF_65)]. It was successful in treating three patients with duodenal perforation, upper-GI vessel leak, and anastomosis leak. This technique do not need multiple and complicated devices for close the perforation and is more effective[[65](#_ENREF_65),[66](#_ENREF_66)]. Nevertheless, the limitations are also obvious. Requesting more time to finish the operation and being clumsy to suture in the gastric fundus make this device needs further improvement. Moran *et al*[[68](#_ENREF_68)] designed a cap-type suturing device based on the natural orifice transluminal endoscopic surgery (NOTES)[[69](#_ENREF_69),[70](#_ENREF_70)]. This suturing device could have the great ability to close the full-thickness perforations effectively and efficiently, compared to most of the other endoscopic devices[[68](#_ENREF_68),[71](#_ENREF_71),[72](#_ENREF_72)]. Mainly consisting of a dual channel, a tissue retractor or a grasping forceps, and a detachable needle tip attached with suture material, it can be used easily. After the grasping forceps grasped one side of the defect, the reloaded needle tip was passed through the tissue surface and then the same operation was done on the other side of the defect. When the grasping forceps retracted, the suture ends are pulled tight to close the defect. In Moran EA’s researches, it was effective and universally adaptable to nearly all kinds of endoscopes which gave us more choices to suture. There are still some requirements to perform it, for example, having a good command of the methods for tying a knot by using this device. Mori *et al*[[73](#_ENREF_73)] had performed a study on 30 excised swine stomachs about properties of their newly innovated devices called DBSS (Double-arm-bar Suturing System). The results showed that the efficacy of DBSS was nearly equal to hand-sewn sutures. Though the OTSC group had better efficacy, according to the statistical result, DBSS could do much better in closing the perforation large than 20 mm.

Although many useful and innovative new endoscopic devices for suturing were reported, large-scale clinical applications have not yet been carried out and the long-term safety and efficacy of those devices need to be further evaluated.

As mentioned above, most of gastrointestinal perforations are iatrogenic and therapeutic endoscopy related perforations are the most important factors. The integrity of gastric mucosa is not consciously emphasized in the current endoscopic resection, which usually leads to mucosal defects and perforation. Recently, we proposed a new method, named as endoscopic mucosa-sparing lateral dissection (EMSLD) for removal of SMT, which not only retained intact mucous membrane but also acquired a good operating field during the procedure. In addition, the retained mucous membrane contributed to the effective closure of the perforation after full-thickness resection for tumor originated from deep layer[[74](#_ENREF_74)]. In our experience, endoscopy doctors should avoid perforation consciously, especially during therapeutic procedure. Sometimes, intentional perforation is necessary for complete removal of tumor. However, the integrity of mucosa should be considered and the retained mucous membrane contributes to successful closure. We have applied this method to close large perforation in four patients until now, and all the perforations were successfully managed(Figure 2).

**CHOICES OF ENDOSCOPIC DEVICES AND TECHNIQUES IN PATIENTS WITH DIFFERENT GASTROINTESTINAL PERFORATIONS**

***Esophageal perforations***

European Society of Gastrointestinal Endoscopy (ESGE) suggests that endoscopic dilations, mucosal resection/submucosal dissection and foreign body removal should be considered to carry an increased risk of esophageal or gastric perforation[[11](#_ENREF_11)]. Most esophageal perforations are iatrogenic. As mentioned above, there are many methods to close esophageal perforations. TTSC is suitable for closing the less than 10mm defect size and OTSC can do well in closing the perforation with a swelling and everted edge or the size requirement is less than 30mm. In addition, esophageal stents show great advantages in handling with the perforations with malignant lesions or stenosis. Endoscopic devices for suturing can be applied in less than 20mm lesions. Attentions should be paid as below: (1) The use of endoscopic techniques may be challenging in the proximal esophagus, due to space constraints and patient intolerance-consider conservative treatment in stable patients; (2) Stent fixation with clip application or suturing techniques may be useful to prevent migration of the stent; and (3) Fibrin glue application have been reported for the closure of esophageal perforations but experiences are limited.

***Gastric*** ***perforations***

Gastric perforations are most often related to therapeutic procedures, including: gastroenteric anastomosis dilation (2%)[[75](#_ENREF_75)]; overdistension during argon plasma coagulation or cryotherapy (< 0.5%); standard snare polypectomy; EMR (0.5%) and more frequently, ESD[[11](#_ENREF_11),[76](#_ENREF_76),[77](#_ENREF_77)]. Compared to esophageal perforations, gastric perforations have much more methods to choose. TTSC clips alone are not recommended for perforations more than 10 mm. In the case of perforations measuring 10-30 mm, the OTSC system has been the most evaluated and should be recommended. If the OTSC technique is unavailable, the combined technique using TTSC clips plus endoloop can be recommended. Innovations and techniques of combining omental patch or nylon rope with clips are also good choices to close over than 10mm defect. Endoscopic suturing is required to close post-ESD defects. Stents is an option to the perforation near the pylorus, or caused by dilating anastomotic stricture. Evidence about endoscopic band ligation for gastric perforations is scarce, which need to be further explored. Attentions should be paid as below: (1) Most perforations of the stomach are small defects that occur during EMR, ESD procedures; (2) Intentional perforation during the endoscopic resection is becoming more and more, and the integrity of mucosa should be emphasized; (3) Closing perforations in proximal stomach may be challenging; and (4) Endoscopic band ligation for gastric perforation closure has been reported but experiences are limited

***Duodenal perforations***

In the case of immediate recognition of perforation, an endoscopic closure should be attempted. This is effective in a minority of cases only (22%)[[11](#_ENREF_11)]. Reports about new devices and techniques for endoscopic closure of duodenal perforations are relatively less. TTSC clips alone are recommended for perforations less than 10mm. In the case of perforations measuring 10-30 mm, TTSC clips combined with endoloops or the OTSC system should be considered. Endoscopic band ligation could be attempted when clips failed, but was not routinely recommended. If the iatrogenic perforation is diagnosed several hours after the endoscopy and the patient shows symptoms of generalized peritonitis and/or sepsis, the only option is surgery. Attentions should be paid as below: (1) The use of transparent cap may be helpful in difficult locations; (2) Closure of medial duodenal wall defects with clips may be challenging due to risk of clipping the ampulla and anatomic location; and (3) Nasoduodenal drain to divert pancreatic and biliary secretions may be beneficial.

***Colonic perforations***

ESGE recommends that complex EMR, ESD, and balloon dilation procedures should be considered to carry increased risk of colorectal perforation. Risk factors include female gender, presumably related to pelvic adhesions, major co-morbidities, inflammatory bowel disease and older age[[78-81](#_ENREF_78)]. As for the strategies to close colonic perforations, TTSC are suitable for closing small holes and OTSC system for larger ones. Clipping plus endoloop can also close large colonic perforations. Endoscopic band ligation is verified to be useful for this type defects, but more evidence are needed. Attentions should be paid as below: (1) Asymptomatic patients with retroperitoneal air alone need no additional treatment; (2) The success rate of endoscopic closure is higher when the perforation is recognized and managed during the same procedure; and (3) Large vertical perforations should be closed from top to bottom, and horizontal perforations should be clipped from left to right.

**Conclusion**

It is sometimes difficult to make a decision which device or technique is the best method for endoscopic closure of gastrointestinal perforations. In general, the decision to attempt endoscopic closure of an iatrogenic perforation depends on multiple factors, including the location, size and the cause of iatrogenic perforation, the endoscopist’s experience and the accessories available at the time. The devices and techniques discussed in this study may not apply in all situations and should be interpreted in the light of specific clinical situations. With the rapid development of new endoscopic devices and techniques, more and more perforations can be well managed by endoscopy. However, more attention should be paid to avoid perforation during endoscopic procedure. Sometimes, intentional perforation is necessary for complete removal of tumor. However, the integrity of mucosa should be considered and the retained mucous membrane can contribute to the successful closure. We introduce and discussed endoscopic devices and techniques in this paper. We hope to provide more information about choosing the appropriate method to close perforations effectively and perfectly. There’s no doubt that further, large, randomized, controlled trials are needed to compare the clinical efficacy of the different endoscopic techniques in every special situation.

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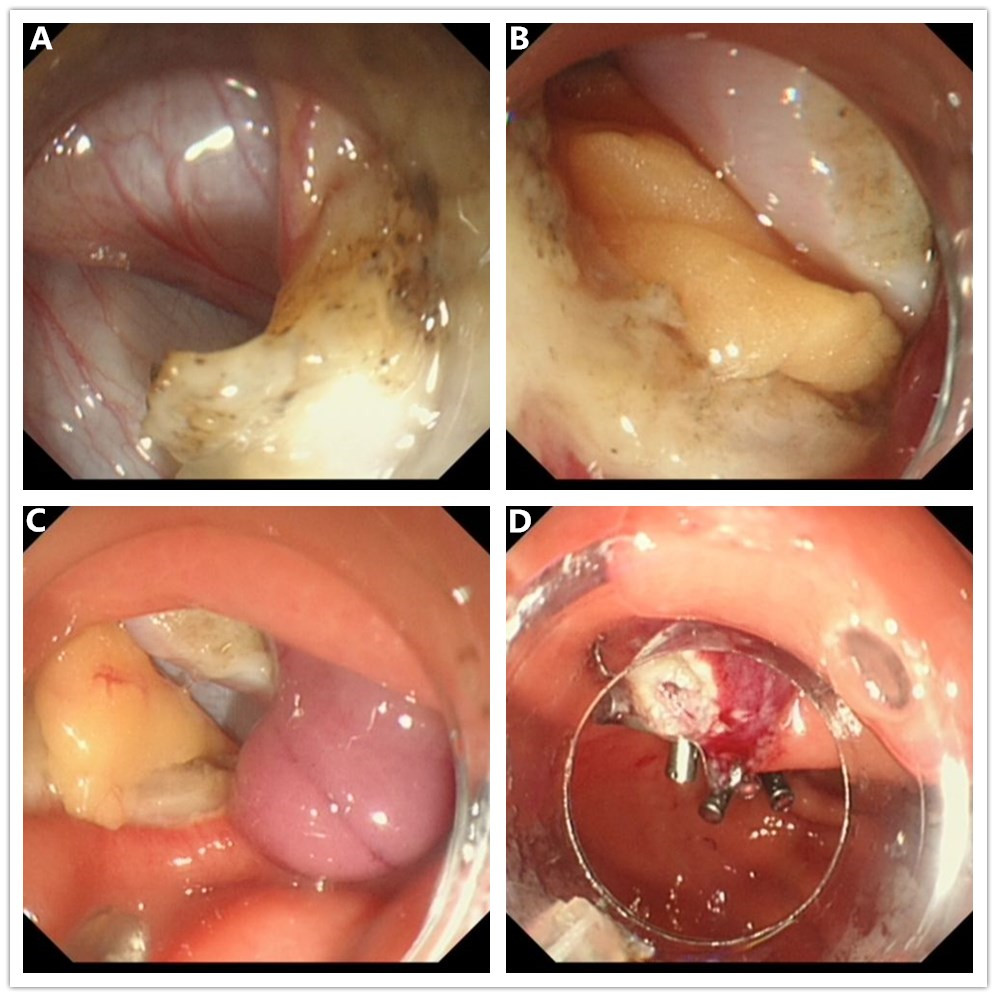
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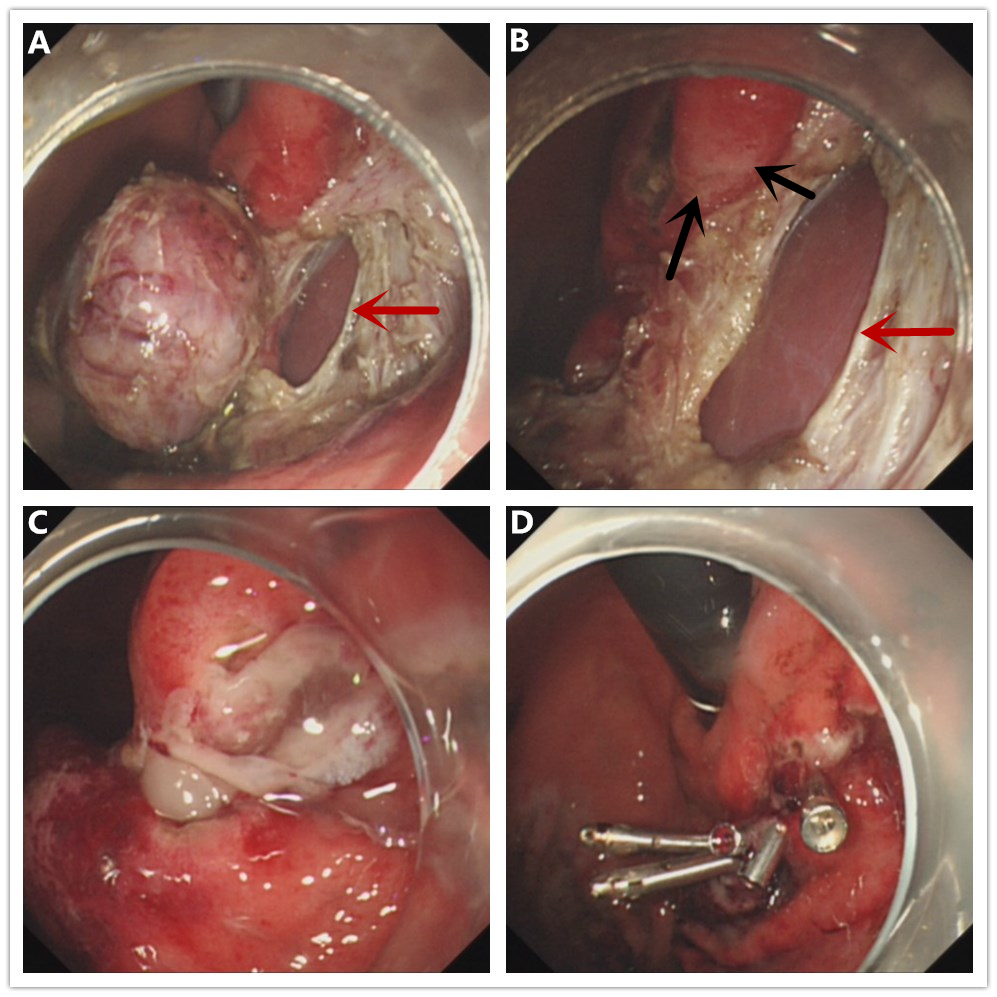
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**Figure 1 over the scope clip system and clips was applied to make successful closure.** A:When ESD was performed for a lesion located in gastric antrum, a large perforation occurred, which was about 30 mm x 15 mm; B:Omentum majus could be seen through the perforated hole; C: It is difficult to make complete closure only by endoclips, and OTSC system was applied to close the perforation. However, partial closure was made because of the perforation was too large; D: Eight endoclips then was used to make the complete closure. ESD: endoscopic submucosal dissection; OTSC: Over the scope clip.

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**Figure 2 to close large perforation in four patients until now, and all the perforations were successfully managed.** A: There was a submucosal tumor located in gastric fundus, which was about 20 mm x 18 mm and originated from deep muscularis propria. An intentional perforation occurred (red arrow) during the procedure for full-thickness resection; B: A larger perforation was left after complete removal of the tumor. However, the mucosa (black arrow) was kept intact; C: We use the retained mucosa to cover over the perforation; D: The wound was covered by the intact mucosa and then was closed with the endoclips.