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2.1 Introduction

The OTSC® system (Ovesco Endoscopy AG, Tübingen, Germany) consists of a nitinol alloy, which allows a high grade of elasticity and was designed to overcome the limitations of traditional through-the-scope (TTS) clips allowing a significantly larger mechanical circumferential compression of large tissue areas, surrounding the vessel without direct trauma.

When released from the applicator, the shape-memory effect and the high grade of elasticity of the nitinol alloy cause closure of the clip. The shape-memory alloy effects a permanent closing force of the OTSCs between 8 and 9 newtons. Because of the superelastic effect of nitinol, the force is permanently applied. Phantom tests and animal survival studies have shown that this closing force is necessary to reach sufficient compression of tissue.

OTSC has shown its encouraging results in management of various clinical situations also critical as the closure of gastrointestinal fistulas, iatrogenic perforations during endoscopy, anastomotic leaks and post bariatric surgery, bleeding lesions, complications and closure of gastrostomies during natural orifice transluminal endoscopic surgery.

Therefore in this chapter we present all the possible applications of the OTSC devices including.

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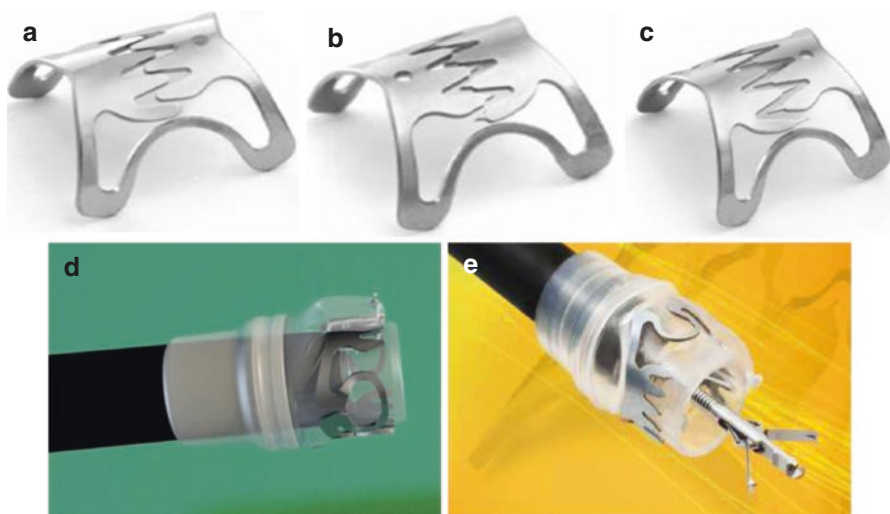


Fig. 2.1 OTSC system. (a) Atraumatic: short teeth for vessels. OTSC. (b) Traumatic regular type: pointed teeth for fistula's wall. OTSC. (c) Traumatic gastric-type clip (gc): longer pointed teeth for gastric wall. OTSC. (d) Atraumatic clip installed on the tip of an endoscope. OTSC (e) the tip of the endoscope loaded with clip and a "twin Gasper" sometimes used to get the tissue

2.2 Technical Concepts

The over-the-scope clip system must be mounted onto the tip of the scope by the applicator with a loading coil, which assists in the opening of the clip. The applicator consists of a cylindrical cap, a wire, and a protection cap. When the clip is opened, it fits to the shape of the cylindrical cap. The cap is mounted onto the tip of the endoscope.

Two different configurations are available: the "atraumatic" version with blunt teeth and the "traumatic" version with two types of sharp teeth ("regular" and "gastric" types) (Fig. 2.1).

The application for bleeding is shown in Fig. 2.2.

The application for the treatment of fistulas is similar, but two types of forceps as shown in Fig. 2.3 can also be used.

2.3 OTSC in GI Bleeding

Gastrointestinal bleeding is a frequent event in clinical practice. Upper gastrointestinal bleeding (UGIB) and lower gastrointestinal bleeding (LGIB) are usually distinguished according to the proximal or distal origin of bleeding with respect to the ligament of Treitz.

Acute UGIB is a common condition worldwide with an estimated annual incidence of 40–150 cases per 100,000 population [3, 4], 4–6 times more frequent than

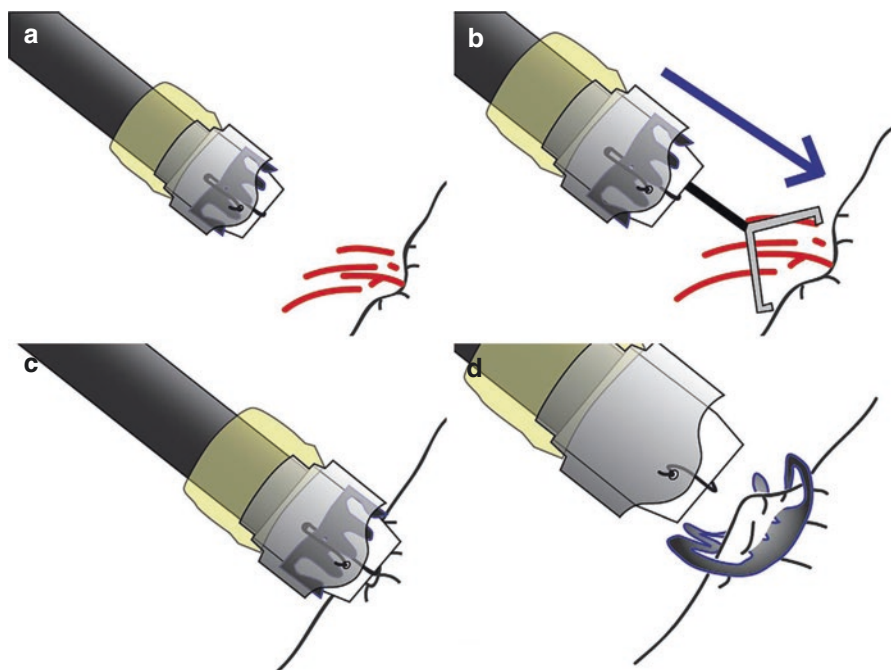


Fig. 2.2 Application procedure. The endoscope is inserted with the mounted and loaded clipping device (a). The tip of the endoscope is adapted to the lesion, with the optional use of application aids like a forceps/grasper, and additional tissue is suctioned into the applicator cap (b). The tissue is in close proximity to the applicator, and the clip is fired by stretching the wire with the hand wheel (c). The clip captures the tissue that is suctioned into the applicator cap, and then it removes the scope from the lesion and proceeds with the correct positioning inspection (d). The arms of the clip protruded approximately 4.5 mm into the lumen of the GI tract



Fig. 2.3 Forceps/graspers: Anchor type (a) twin type (b)

Table 2.1 Most common causes of UIGB

	%
Peptic ulcer	28–59
Erosive	1–47
Variceal bleeding	4–20
Esophagitis	3–12
Mallory–Weiss	4–7
Neoplasm	2–4
Others (Dieulafoy’s lesions, angiodysplasias, gastric antral vascular ectasia, portal hypertensive gastropathy)	2–7
None	16–20

LGIB; it frequently leads to hospital admission and has significant associated morbidity and mortality, especially in the elderly. The most common causes of acute UGIB are nonvariceal UGIB (NVUGIB) [3, 4]. This includes peptic ulcers, 28–59 % (duodenal ulcer 17–37 % and gastric ulcer 11–24 %); mucosal erosive disease of the esophagus/stomach/duodenum, 1–47 %; Mallory–Weiss syndrome, 4–7 %; upper GI tract malignancy, 2–4 %; other diagnoses, 2–7 %; or no cause identified, 7–25 % [3, 4]. Moreover, in 16–20 % of acute UGIB cases, the cause of bleeding is multifactorial (Table 2.1).

LGIB is less common than UIGB, and the incidence is approximately 36 per 100,000 population [5] with a mortality of up to 3.9 % within 1 year [6, 7], although this may rise as high as 13 % by 5 years [8]. The mean age at presentation is in the range 63–77 years [9]. Up to 85 % of patients have self-limiting episodes [10], but re-bleeding can occur in up to 19 % of cases within a year [8].

The commonest cause of lower GI bleeding requiring hospital admission is diverticulosis, accounting for approximately 20–40 % of the cases [8], as well as more than 50 % of re-bleeding admission [12]. Right-sided diverticulitis is particularly likely to cause bleeding [13]. Ischemic colitis is the second most common cause, representing 12–16 % of cases [13, 14]. Common causes also include hemorrhoids and carcinomas of the colon and rectum [12]. Less common causes are bleeding following polypectomy, inflammatory bowel disease, and infective colitis. A few cases are due to radiation proctitis. Angiodysplasias are less common, but the source of these can be in the small bowel, and bleeding is often severe in such cases [11].

Endoscopic therapy for active UGIB can dramatically reduce the risk of re-bleeding or ongoing bleeding, the need for surgery, the number of units of packed erythrocytes required for transfusion, and the length of hospital stay [15, 16].

The goal of therapeutic endoscopy in patients with UGIB is to stop bleeding and prevent re-bleeding.

Endoscopic techniques include injection therapy, ablative therapy, and mechanical therapy. Commonly and less commonly used and experimental therapies for NUGIB are reported in Table 2.2.

Table 2.2 Endoscopic therapies for NUIGB

Common therapies for nonvariceal UGIB	Uncommon therapies for nonvariceal UGIB
<i>Injection therapy</i>	<i>Injection therapy</i>
<i>Dilute epinephrine</i>	<i>Normal saline</i>
<i>Sclerosants</i>	<i>Thrombin</i>
<i>Ablative therapy</i>	<i>Fibrin sealant</i>
<i>Contact methods</i>	<i>Cyanoacrylate glue</i>
<i>Thermocoagulation—heater probe</i>	<i>Ablative therapy</i>
<i>Electrocoagulation—BICAP, Gold Probe™</i>	<i>Cryotherapy</i>
<i>Noncontact methods</i>	<i>Photocoagulation—Nd:YAG laser</i>
<i>Argon plasma coagulation</i>	<i>Mechanical therapy</i>
<i>Mechanical therapy</i>	<i>Detachable snare—Endo-loop™ (Olympus Corporation, Lake Success, NY)</i>
<i>Hemoclips</i>	<i>Suturing device</i>
<i>Band ligation</i>	<i>Dual-therapy devices</i>
	<i>Probe combining electrocautery with needle injection</i>
	<i>Device combining electrocautery with mechanical therapy</i>
	<i>Topical therapy</i>
	<i>Hemospray</i>
	<i>Endoclot</i>

Although several types of endoscopic treatment for bleeding peptic ulcers have been described, including injection therapy, thermal coagulation, hemostatic clips, fibrin sealant (or glue), argon plasma coagulation, and combination therapy (typically injection of epinephrine combined with another treatment modality), relatively a few prospective comparative trials have been performed. Currently, most patients are treated with either thermal coagulation therapy or hemostatic clips, with or without the addition of injection therapy.

Meta-analyses have shown that combination endoscopic therapy (dilute epinephrine injection combined with a second hemostasis modality including injectable, thermal contact probe, or clips) is superior to injection therapy alone, but not to clips or contact thermal therapy alone [17, 18]. There may be practical reasons to pre-inject dilute epinephrine before other therapies for high-risk endoscopic stigmata. Injection of epinephrine may slow or stop bleeding allowing improved visualization for application of subsequent therapy. Adverse events associated with combination endoscopic hemostasis are infrequent and include induction of bleeding (1.7 %) and perforation (0.6 %) [18].

Recent international consensus guidelines recommend combination therapy (dilute epinephrine injection combined with contact thermal therapy, clips, or injection of a sclerosant) as appropriate treatment in patients with peptic ulcer bleeding with high-risk endoscopic stigmata [19–21].

Despite major advances in its management over the past decade, including intravenous high-dose proton pump inhibitors, NVUGIB is still associated with considerable morbidity, mortality, and health economic burden [22]. Of particular note is re-bleeding, a major predictor of morbidity and mortality that has not been

significantly improved according to data registered in the last 15 years [4, 23]. Although huge advances have been made in terms of therapeutic endoscopic devices, complete hemostasis of complicated lesions (i.e., large vessels or fibrotic ulcers) still represents a challenging task.

Mechanical or thermal therapy fails to stop bleeding in 5–12% of cases [18, 24]. The limits of current endoscopic therapies are linked to different variables such as type, size, and location of the lesion and exposed large vessels. High-risk lesions may be technically difficult to manage, resulting in failure of endoscopic treatment.

From a technical point of view, the limits of hemoclips application are well known. The limited diameter of the working channel of the endoscope results in a relatively small size of through-the-scope clips allowing compression of limited amounts of tissue, especially in the presence of scarred and hardened tissue or inflammatory mucosa. Accordingly, the hemostatic effect may not be sufficient for large-size vessels, and there is often the need to apply more than one clip to achieve an effective hemostasis [25, 26]. Furthermore correct application in the antrum and duodenal bulb is technically challenging [27].

Preliminary data suggested a possible role of OTSC in GI bleeding. Kirschniak et al. [28] treated 12 patients with upper GI bleedings; most of them were caused by peptic ulcer disease. Primary hemostasis was achieved in all cases. In two cases, a secondary bleeding occurred. In one case, it was observed 12 h after OTSC treatment of a Mallory–Weiss lesion, and in the other case, it occurred 7 days after treatment of bleeding duodenal ulcer. This study demonstrated the efficacy of OTSC in upper GI bleeding; however, authors did not specify the characteristics of the lesions treated in terms of Forrest classification, location, and size, debarring the assessment of its possible advantage versus standard endoscopic therapy.

A recent study demonstrated efficacy and safety of the OTSC for the treatment of patients with severe acute upper and lower GI bleeding unresponsive to conventional treatment, resulting in a salvage endoscopic treatment during NVUGIB emergencies [29]. In that study, 23 cases with GI bleeding unresponsive to conventional endoscopic treatment modalities were treated with OTSC. Primary hemostasis with OTSC was achieved in 22/23 patients. In one patient with a posterior wall duodenal ulcer, emergency-selective radiological embolization was required to stop bleeding after failure of the OTSC procedure. Re-bleeding was observed in two cases; both cases were successfully re-treated endoscopically. Authors concluded that OTSC is an effective and safe endoscopic tool for treatment of patients with severe acute NVUGIB unresponsive to conventional treatment modalities, although the proportion of high-risk patients was not stated.

These data were confirmed in two recent studies. One study reported 12 patients with severe gastrointestinal bleeding due a duodenal ulcer ($n=6$), gastric ulcer ($n=2$), Dieulafoy's lesion ($n=2$), anastomotic ulceration ($n=1$), and Mallory–Weiss tear ($n=1$). All patients had failed hemostatic therapy using traditional endoscopic methods. Hemostasis was achieved in all patients. REBLEEDING occurred in two patients 1 day after OTSC placement. Subsequently, the patient with a Mallory–Weiss tear was successfully treated with an injection of saline/epinephrine and the placement of conventional clips. The patient with gastrojejunal anastomotic ulcers

was readmitted with melena 7 days after placement of the OTSC. Repeat EGD showed active bleeding from a large, circumferential ischemic anastomotic ulcer. No endoscopic intervention was undertaken, and the patient proceeded to radiological embolization and then to surgery for reconstruction of the anastomosis. There were no complications associated with the application of OTSCs [30].

The second recent study reported a series of a total of nine patients. Six of them had undergone previous endoscopic hemostasis therapy. The median size of the ulcers was 2.5 cm. All the ulcers and tumors demonstrated the presence of a visible vessel on endoscopy. The technical success rate of OTSC was 100%, and endoscopic hemostasis was achieved in all patients. Two patients experienced re-bleeding, which required further intervention, and hence, the clinical effectiveness was 78% [31]. In these two studies, the authors concluded that OTSC should be considered in patients with refractory bleeding after failure of conventional methods of endoscopic hemostasis, before surgery or angiographic embolization. Analyzing the results of these two studies, we could suppose that previous endoscopic treatment, i.e., clip, could hamper OTSC application resulting in re-bleeding.

Another case series reported the utility of OTCS to provide endoscopic hemostasis for bleeding posterior duodenal ulcers [32]. In this study, four patients with massive gastrointestinal bleeding due to ulcers located in the posterior bulb and actively oozing were treated with OTSC after failure of initial therapy with injection of epinephrine/saline solution and clip placement. Hemostasis was successfully achieved in all four cases. The authors concluded the OTSC is effective for obliterating ulcers with bleeding vessel located in a difficult position (i.e., the posterior duodenum); although heater probe is an effective alternative method to treat such lesions, this treatment modality is available in the USA and some Asian countries only but not in most European countries. However, using a heater probe can result in a higher risk of perforation [33]. The authors also claimed that the placement of OTSC was easy [32].

A more recent study reported a series of patients in whom OTSC represented the first-line endoscopic treatment in patients with high-risk nonvariceal upper gastrointestinal bleeding [34]. During the study period, 40 consecutive patients with severe acute NVUGIB were treated with OTSC as first-line endoscopic treatment. Indications for OTSC treatment included gastric ulcer with large vessel (Forrest IIa) ($n=8$, 20%), duodenal ulcer (Forrest Ib) ($n=7$, 18%), duodenal ulcer with large vessel (Forrest IIa) ($n=6$, 15%), Dieulafoy's lesion ($n=6$, 15%), and other secondary indications ($n=13$, 32%). Sixteen (40%) patients had gastric or duodenal ulcer [20 mm (20–29 mm: $n=10$, 25%); 30 mm: $n=6$, 15%]. Technical success and primary hemostasis were achieved in all patients (100%). None of the patients had re-bleeding or required surgical or radiological embolization treatment. No other complications were observed during the 30-day follow-up period. The authors concluded that OTSC placement represents a first-line endoscopic treatment being effective, safe, and technically easy to perform.

In summary, OTSC system utilizes a very contractile, superelastic nickel titanium alloy, which provides tissue apposition that is far superior to that of traditional clipping. Based on published data, the OTSC system appears promising for

the treatment of bleeding lesions with large-diameter visible vessels, challenging high-risk bleeding lesions such as Dieulafoy's lesion or those located in awkward positions, such as the greater curvature of the stomach or the posterior duodenal wall or which may not always be amenable to treatment with standard endoscopic devices.

It is believed that hemostasis is achieved by a combination of two mechanisms: (I) sealing the blood vessel and (II) closing an ulcer. However, the main mechanism appears to be "tissue compression," which occurs by compressing the surrounding tissue around the vessel. However even if it is possible to close an ulcer by applying the OTSC directly on a bleeding vessel, it is believed that the abovementioned "tissue compression" mechanism better explains the hemostatic mechanisms.

Moreover, most gastroscopes have working channels on the left side making it difficult to apply endoscopic hemostasis to lesions located on the right or in the posterior duodenum. In addition, standard clips often fall off from these lesions and also induce more bleeding by lacerating the vessel.

The duration of the clipping procedure itself depends on the ability to get in touch with the lesion and sufficient adaptation of the applicator cap to the lesion. The correct and secure application of the OTSC depends on the correct fitting of the application cap to the lesion. With the help of application aids like forceps or graspers, the lesion can be fixed, and then the scope can be pushed onto the lesion. Because there is no visualization possible at the moment of application, the endoscopist must be sure to be in the correct position.

Despite the early promising results regarding the OTSC device, we need more prospective clinical trials to demonstrate its superiority relative to traditional clips and closure devices.

Nevertheless, it is clear that the OTSC system is already part of the therapeutic armamentarium of the advanced endoscopist, and we expect this device to be used more frequently in clinical practice.

2.4 The New Device DC ClipCutter

A potential complication of the OTSC system is that once it is deployed it cannot be removed. Some publication has recently demonstrated three rescue methods to remove the clip in case of misapplication [35–37].

The "official device" of Ovesco Endoscopy AG is the DC ClipCutter: the clip is locally brought to the melting point through the application of a brief pulse of current.

The remOVE DC System consists of three units: (Fig. 2.4)

- A. remOVE Impulse DC (DC generator)
- B. remOVE DC Cutter (bipolar endoscopic instrument)
- C. remOVE Securcap (cap for the safe extraction of the clip fragments)

Until now, in addition to some report stated on the porcine model [38], only one paper has been published with the application in humans [39]. A total of 11 patients underwent endoscopic removal of an OTSC. The clip was cut at two opposing sites



Fig. 2.4 The remOVE DC system (a) The cutter clipping the clip during the cutting (b)

by a prototype of DC ClipCutter getting the success rate, to complete the cutting and removal in 91 % of cases.

No major complications were observed.

2.5 Performance of Over-The-Scope Clip System in the Endoscopic Closure of Iatrogenic Gastrointestinal Perforations and Postsurgical Leaks

Over the years, the absolute number of diagnostic and especially therapeutic endoscopies has grown tremendously.

Endoscopic technological developments led to the performance of more advanced therapeutic procedures with higher risk of complications [40].

Surgeons also began to perform more complex gastrointestinal interventions. Consequently, endoscopists are increasingly facing gastrointestinal (GI) defects, such as anastomotic leaks, fistulas, and perforations. Anastomotic leak is defined as disruption at a surgical anastomosis resulting in a fluid collection, fistula is defined as abnormal communication between a natural or pathological cavity with the external or two natural cavities between them, and perforation is defined as an unintentional, acute iatrogenic, full-thickness defect in the GI tract [41, 42].

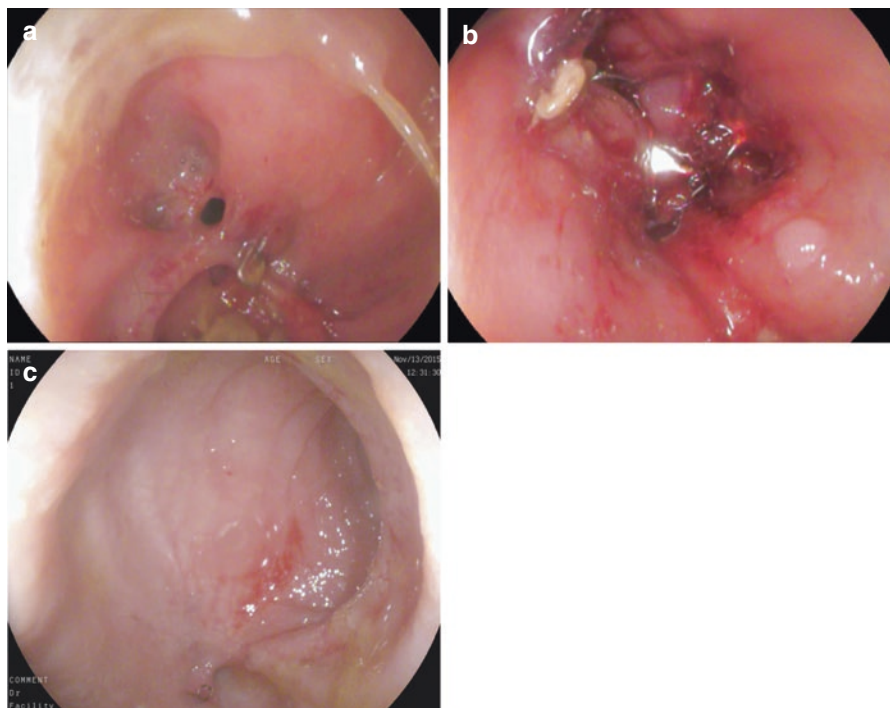


Fig. 2.5 (a) Perianastomotic fistula. (b) The OTS clip positioned to closing the fistula. (c) After 2 months, the fistula completely healed

Surgical treatment has been the mainstay of therapy for GI defects. However, surgical repair, especially for perforations, is associated with higher morbidity (25–36%) and mortality (7–10%) risks, which are accompanied by the risks of general anesthesia, prolonged recovery, and increased costs [43–46].

Therefore, endoscopic management of these complications is gaining more popularity and became a good option in selected cases.

Several endoscopic techniques have been described for closure of GI defects by using several devices, such as clips, endoloops and rubber bands, and fibrin glue, and methods, such as plugging by a prolene mesh and application of cyanoacrylate and placement of covered self-expandable metal stents (CSEMSs) or self-expandable plastic stents [47–51]. However, the success rate of these procedures varies between 55 and 69%, and additional surgical management is often required [52]

More recently the placement of a new endoscopic Over-The-Scope Clip (OTSC®) system (Ovesco Endoscopy GmbH, Tübingen, Germany) has been described as illustrated above. The GI defect is suctioned into the cap, and the clip is then deployed, approximating the edges (Fig. 2.5). The OTSC device also contains two types of grasping forceps that can be inserted through the operative channel of the scope and used to pull both tissue edges into the cap before the clip released (Fig. 2.3). The use of OTSC has some advantages and limitations. The first

technical limitation of OTSC system is large diameter, until 12 mm, that in patient with GI defect and endoluminal stenosis does not allow passage of the scope with mounted devices. Another limitation, compared to the through-the-scope (TTS) clips, is that in cases of necessity to place two or more devices, it is mandatory to remove every time the scope and proceed to assembly a new system. The advantages of OTSC over TTS devices are the larger defects that can be closed by one clip (limited by cap diameter and flexibility of the tissue being pulled into the cap) and the greater compression and higher closure force. The OTSC system also has a higher rate of full-thickness closure, therefore an improved safety profile with regard to closure-related infectious complications.

Clinical experience shows that clips usually fall off after several weeks or months, depending on the amount of tissue grasped. Since OTSC clips are fully biocompatible, they may stay in place indefinitely and does not subsequently preclude magnetic resonance imaging [53].

Complications with the use of OTSC device are rare; isolated cases of esophageal perforation, acute cholangitis, inadvertent tongue piercing, and intestinal obstruction (from accidental inclusion of opposing walls into the OTSC) have been reported [54–57].

2.6 Perforation

Perforation is the most feared adverse event of GI endoscopy, and its incidence varies depending on multiple patient-related and procedure-related factors [58, 59].

With more advanced interventional endoscopic procedures, endoscopists may be faced more often with perforations; indeed most cases of iatrogenic perforations occur during therapeutic procedures. The reported perforation rates are 0.3–0.5 % in endoscopic mucosal resection (EMR) and 4–10 % in endoscopic submucosal dissection (ESD) [60].

The standard treatment for acute endoscopic perforations is surgical repair. However, immediate endoscopic closure is less invasive, does not require anesthesia, and minimizes leakage of GI contents.

The OTSC system can capture and close larger defects up to 30 mm. From the technical point of view, the setting of acute endoscopic perforation is optimal for OTSC use: the lesion is fresh and without fibrotic alterations or inflammation. Until now, no randomized controlled clinical study has been performed to compare the OTSC system with other approaches. Several case series have demonstrated successful use of the OTSC in closure of acute perforations with clinical success rates ranging from 65 to 100 % in healing the GI defect (Table 2.3) [28, 54, 56, 61–71]. The largest numbers of patients with gastrointestinal perforations treated with OTSC have been reported in two multicenter studies. Voermans et al. reported successful closure without need for surgery in 32 of 36 patients (89 %) with acute iatrogenic perforations of the gastrointestinal tract <3 cm in size within 24 h of onset of perforation [56]. Recently, Haito-Chavez et al. published a multicenter international retrospective study of 188 patients who underwent attempted OTSC

Table 2.3 Studies reporting over-the-scope clip closure of gastrointestinal perforation

Author	Year	Study design	Number	Overall success (%)	Size of defect
Kirschniak et al. [22]	2007	Retrospective	4	4/4 (100 %)	4–8 mm
Repici et al. [23]	2009	Retrospective	2	2/2 (100 %)	N.S.
Seebach et al. [4]	2010	Retrospective	4	3/4 (75 %)	N.S.
Kirschniak et al. [24]	2011	Retrospective	11	11/11 (100 %)	N.S.
Sandmann et al. [25]	2011	Retrospective	3	3/3 (100 %)	N.S.
Baron et al. [15]	2012	Retrospective	5	4/5 (80 %)	N.S.
Gubler et al. [26]	2012	Prospective	14	13/14 (93 %)	6–30 mm
Hagel et al. [27]	2012	Retrospective	17	11/17 (65 %)	2–40 mm
Voermans et al. [17]	2012	Prospective	36	32/36 (89 %)	N.S.
Nishiyama et al. [28]	2013	Retrospective	11	10/11 (90 %)	5–40 mm
Schlag et al. [29]	2013	Prospective	6	6/6 (100 %)	7–30 mm
Changela K et al. [30]	2014	Retrospective	3	3/3 (100 %)	20 mm
Haito- Chavez et al. [31]	2014	Retrospective	40	36/40 (90 %)	7 mm (median)
Farnick et al. [32]	2015	Prospective	18	15/18 (83 %)	1–30 mm

placement for GI defects, and in the 40 cases with perforation analyzed, technical success was achieved in 39 cases (97.5 %), immediate clinical success was achieved in 37 (94.9 %), and 36 patients (90 %) had a long-term clinical success [70].

The position paper for diagnosis and management of iatrogenic perforation occurring during diagnostic or therapeutic digestive endoscopic procedures of the European Society of Gastrointestinal Endoscopy (ESGE) recommends the use of OTSC system as first-line therapy for large esophageal (<20 mm) gastric (<30 mm), duodenal, and colonic perforations [72].

2.7 Postsurgical Leaks

Anastomotic and staple line leaks occur in 0.4–5.2 % of patients having Roux-en-Y gastric bypass, 1.6–13.6 % of patients undergoing gastric resection for malignant neoplasms, and 3–33 % of patients having a colon resection for colorectal cancer [73–79]

Postsurgical complications such as fistula and leaks are conventionally submitted to surgical repair. However, surgical re-intervention has a significant morbidity and mortality, prolongs hospital stay, and increases costs [80]

The main goal of endoscopic therapy is the interruption of the flow of luminal contents across a gastrointestinal defect. Covered removable SEMS and OTSC are recent innovations that provide minimally invasive closure. Most of the stents usually used for the management of leakages in benign indications are fully covered in order to optimize removability. It results in a high migration rate with risk of recurrence [51].

Table 2.4 Studies reporting Over-The-Scope Clip closure of postsurgical leak

Author	Year	Study design	Number	Overall success (%)	Size of defect
Parodi et al. [42]	2010	Prospective	6	4/6 (67 %)	10–20 mm
Pohl et al. [43]	2010	Retrospective	2	1/2 (50 %)	N.S.
Seebach et al. [4]	2010	Retrospective	3	2/3 (67 %)	N.S.
Albert et al. [44]	2011	Retrospective	6	5/6 (83.3 %)	N.S.
Sandmann et al. [25]	2011	Retrospective	3	2/3 (67 %)	N.S.
Manta et al. [45]	2011	Retrospective	12	11/12 (92 %)	6–25 mm
Surace et al. [46]	2011	Prospective	18	7/18 (39 %)	N.S.
Arezzo et al. [47]	2012	Prospective	10	6/10 (60 %)	6–12 mm
Baron et al. [15]	2012	Retrospective	3	1/3 (33 %)	N.S.
Disibeyaz et al. [48]	2012	Retrospective	5	3/5 (57 %)	6–20 mm
Galizia et al. [49]	2012	Retrospective	3	3/3 (100 %)	N.R.
Menningen et al. [50]	2013	Retrospective	6	5/6 (83 %)	<20 mm
Haito-Chavez et al. [31]	2014	Retrospective	30	22/30 (73.3 %)	8 mm (median)
Winder et al. [51]	2015	Retrospective	6	6/6 (100 %)	8 mm (median)
Farnick et al. [32]	2015	Prospective	16	9/16 (56 %)	1–30 mm

The successful closure of leaks with OTSC has varied widely between 33 and 100 % in published series (Table 2.4) [54, 63, 64, 70, 71, 81–91]. Difficulties arise in the treatment of chronic leaks. The failure of this technique is more frequent when the leak edges are fibrotic and in patients who had undergone several surgical approaches. Indeed, Albert et al. found that success was high and durable when the time from diagnosis to application of the clip was within 1 week, resulting in a success rate of 100 % in postoperative lesions [44]. With increasing time from detection of the lesion to endoscopic treatment, the tissue was more difficult to grasp, and the success rate decreased to less than 60 % [44]. Haito-Chavez et al. analyzed 30 cases with long-term follow-up of OTSC placement for leaks, and technical success was achieved in 27 patients, immediate clinical success was achieved in 26 patients (96.3 %), and the overall long-term clinical success was achieved in 22 patients (73.3 %) [31]. In the three cases without technical success, the fibrotic or necrotic borders were cited as the most common cause of failure [70]

2.8 Gastrointestinal Fistulas

Gastrointestinal fistulas occur after surgical intervention, secondary to inflammatory or infectious disorders, after radiation therapy, or following removal of percutaneous tubes [91].

Despite the advent of the OTSC system, closure of GI fistulas using endoscopic methods remains difficult, and the successful closure of fistulas varies between 25 and 100 % in published series (Table 2.5) [54, 63, 64, 70, 71, 81–90]. A systematic review by Weiland et al. evaluated several studies using the OTSC system for

Table 2.5 Studies reporting Over-The-Scope Clip closure of gastrointestinal fistulas

Author	Year	Study design	Number	Overall success	Size of defect
Parodi et al. [42]	2010	Prospective	3	3/3 (100 %)	10–15 mm
Albert et al. [44]	2011	Retrospective	4	1/4 (25 %)	N.S.
Kirschniak et al. [24]	2011	Retrospective	8	3/8 (37.5 %)	N.S.
Sandmann et al. [25]	2011	Retrospective	4	4/4 (100 %)	N.S.
Arezzo et al. [47]	2012	Prospective	4	4/4 (100 %)	5–12 mm
Baron et al. [15]	2012	Retrospective	14	10/17 (59 %)	N.S.
Disibeyaz et al. [48]	2012	Retrospective	3	1/3 (33 %)	10–15 mm
Nishiyama et al. [28]	2013	Retrospective	4	3/4 (75 %)	10–28 mm
Menningen et al. [50]	2013	Retrospective	8	6/8 (75 %)	N.S.
Haito-Chavez et al. [31]	2014	Retrospective	30	33/91 (42.9 %)	5 mm (median)
Winder et al. [51]	2015	Retrospective	17	17/22 (77.3 %)	5 mm (median)
Law et al. [52]	2015	Retrospective	27	25/47 (53 %)	N.S.

endoscopic closure of GI fistulas and reported a high rate of technical success (84.6 %) but a durable clinical success of 69 % [92].

Haito-Chavez et al. reported the results of the OTSC system for the treatment of GI fistula in 91 patients with a median follow-up of 121 days, and technical success was achieved in 85 patients (93.4 %), immediate clinical success was achieved in 77 patients (90.6 %), and the overall long-term clinical success was achieved in only 39 patients (42.9 %) [90].

Law et al. in a retrospective review of 47 patients, who underwent OTSC placement for closure of GI fistulas, reported an initial technical success of 89 % (42/47 cases) but an overall long-term clinical success achieved in only 25 cases (53 %) [91].

The induration and fibrosis associated with chronic fistulas may result in failure of adequate tissue apposition. Adjunctive measures have been evaluated in addition to OTSC placement to promote fistula closure. Attempts to denude or disrupt the epithelialized tract by mechanical (e.g., standard cytology brush) or thermal (e.g., argon plasma coagulation) processes have been described and might hinder optimal OTSC opposition and successful fistula closure [54, 70, 93]. The OTSC system may be effective in combination with adjunctive therapies, such as covered SEMS placement and application of cyanoacrylate or other tissue adhesives, to resolve the underlying disorder [54, 90, 93].

2.9 Over-The-Scope Clip Full-Thickness Resection Device (OTSC FTRD)

The novel “full-thickness resection device” (FTRD, Ovesco Endoscopy, Tübingen, Germany) is the first combined system for full-thickness resection of colon lesions with the closure and resection of the tissue integrated in a single procedure.



Fig. 2.6 OTSC FTRD system. (a) Cap with preloaded clip, (b) FTRD system assembled, mounted and ready for use. (c) Forceps to grasp the tissue introduced into the working channel. (d) Lesion pulled into the cap with forceps. (e) The Over-The-Scope Clip deployed; and the tissue above the clip resected

The OTSC FTRD was designed for one-step colon endoscopic FTR (EFTR) after OTSC application. Similar to the OTSC system, it can be mounted over a standard colonoscope and consists of a long transparent applicator cap carrying a modified 14 mm OTSC. The FTRD system is shown in Fig. 2.6. Compared to the conventional OTSC system, the cap is much longer (23 mm vs. 6 mm) and can therefore incorporate more tissue.

A 13 mm monofilament high-frequency (HF) snare is a preloaded on the tip of the cap. The handle of the snare runs on the outer surface of the scope underneath a plastic sheath. For resection, grasping forceps (or a tissue anchor) are advanced

through the working channel of the scope; the lesion is pulled into the cap thereby creating a full-thickness duplication of the colonic wall.

Immediately after clip deployment, the tissue above the clip is resected with the snare above the clip. The device was firstly introduced in 2011 and evaluated in several porcine studies [94–97].

To date, there are five published studies, the first reporting successful EFTR of three recurrent non-lifting colonic adenomas [98]. A video case has been published demonstrating successful EFTR of an adenoma arising from a diverticulum [99].

A case series concerning 25 patients who underwent EFTR in the colon and rectum has recently been reported: immediate or delayed perforation or major bleeding was not reported. Technical success was 83.3% and R0 resection rate 75% [100].

In all series published, the majority of indications were non-lifting adenomas, or the recurrences and the sites were everywhere in the colorectum. Other indications are the resection of small subepithelial tumors in different locations with a mean tumor size of 15 mm.

A published data suggest that the FTRD system is feasible, effective, and safe. The major limitation of the system is the maximum size of the lesion to be resected. It is true that this limit strongly depends on the mobility of the colonic wall; indeed a resection specimen of up to 5.4 cm has been reported in experimental porcine study colon [94], while the median diameter in the mentioned clinical study was 24 mm (range 12–40 mm) [100].

This technique represents a minimally invasive endoluminal approach, which could become the ideal treatment for lesions with low risk of tumor seeding like advanced adenomas, “small” mesenchymal tumors, even a subset of early carcinomas, or neuroendocrine tumor [101, 102].

The advantages are:

- To allow to evaluate and get properly the R0 resection in T1 lesions with infiltration of the submucosa
- Give the option to safely and completely remove small submucosal lesions
- Having the possibility to get full-thickness intestinal biopsies

However some disadvantages are:

- Lower maneuverability of the colonoscope with the mounted device, so sometimes it is difficult to achieve proximal lesions
- Limits of size related to the diameter of the device
- Applicability only in the colon, because pharyngeal intubation would be dangerous and the gastric wall thickness does not allow a complete resection “full thickness”

The limit of the size of the device involves:

- (a) The difficulty to resect larger lesions or hard scar tissue.
- (b) The difficulty to evaluate well the wound edges with the risk of an R1 resection

In this context, until now, the percentage of R0 resections are around 75 % vs. 88 % of endoscopic submucosal dissection (ESD) [103]

At this point, it should be stated that all innovative techniques need to be investigated systematically. The majority of available studies are preclinical with a very limited amount of animal models or retrospective noncontrolled small clinical series; surely this depends partly because the device is recent. However, it is known that in Germany there are some prospective multicenter and single-center ongoing studies [104].

Conclusions

In summary, the recent developments and studies have brought the OTSC system into clinical routine for selected indications. While the role of OTSC system is widely accepted and there are many published literature for application in fistulas and bleeding, the EFTR system has yet to be widely applied in order to take stock of cost benefit.

This progress has again pushed the frontiers of endoluminal resections toward transmural interventions. However, prospective clinical trials are necessary to define applications and technical improvements regarding resection/closure devices and platforms.

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