

# World Journal of *Gastroenterology*

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**ABOUT COVER**

Editorial board member of *World Journal of Gastroenterology*, Dr. Ji is a Distinguished Professor in Shanghai University of Traditional Chinese medicine, Shanghai, China. Having received his Bachelor degree from Yangzhou College of medicine in 1991, Dr. Ji undertook his postgraduate training first at Hubei College of Traditional Chinese medicine, received his Master degree in 1994, and then at Shanghai University of Traditional Chinese medicine, received his PhD in 1997. He became Chief Physician in the Gastroenterology Division, Longhua Hospital affiliated to Shanghai University of Traditional Chinese medicine since 2004. His ongoing research interests are applying Evidence-based medicine methods to study the effects, and managing the disease-syndrome pattern establishment of integrative medicine on digestive diseases. Currently, he is the President of the Shanghai Association for the Study of the Liver with integrative medicine.

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## Clinical efficacy of the over-the-scope clip device: A systematic review

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### Abstract

#### BACKGROUND

The over-the-scope clip (OTSC) system has been increasingly utilized as a non-surgical option to endoscopically manage refractory gastrointestinal (GI) hemorrhage, perforations/luminal defects and fistulas. Limited data exist evaluating the efficacy and safety of OTSC.

#### AIM

To determine the clinical success and adverse event (AE) rates of OTSC across all GI indications.

#### METHODS

A PubMed search was conducted for eligible articles describing the application of the OTSC system for any indication in the GI tract. Any article or case series reporting data for less than 5 total patients was excluded. The primary outcome was the rate of clinical success. Secondary outcomes included: Technical success rate, OTSC-related AE rate and requirement for surgical intervention despite OTSC placement. Pooled rates (per-indication and overall) were calculated as the number of patients with the event of interest divided by the total number of patients.

#### RESULTS

A total of 85 articles met our inclusion criteria ( $n = 3025$  patients). OTSC was successfully deployed in 94.4% of patients ( $n = 2856/3025$ ). The overall rate of clinical success (all indications) was 78.4% ( $n = 2371/3025$ ). Per-indication clinical success rates were as follows: (1) 86.0% (1120/1303) for GI hemorrhage; (2) 85.3% (399/468) for perforation; (3) 55.8% (347/622) for fistulae; (4) 72.6% (284/391) for anastomotic leaks; (5) 92.8% (205/221) for defect closure following endoscopic resection (*e.g.*, following endoscopic mucosal resection or endoscopic submucosal dissection); and (6) 80.0% (16/20) for stent fixation. AE's related to the deployment of OTSC were only reported in 64 of 85 studies ( $n = 1942$  patients), with an overall AE rate of 2.1% ( $n = 40/1942$ ). Salvage surgical intervention was

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required in 4.7% of patients ( $n = 143/3025$ ).

## CONCLUSION

This systematic review demonstrates that the OTSC system is a safe and effective endoscopic therapy to manage GI hemorrhage, perforations, anastomotic leaks, defects created by endoscopic resections and for stent fixation. Clinical success in fistula management appears limited. Further studies, including randomized controlled trials comparing OTSC with conventional and/or surgical therapies, are needed to determine which indication(s) are the most effective for its use.

**Key words:** Over-the-scope clip; Hemostasis; Perforation; Fistula closure; Endoscopic resection; Anastomotic leak; Ovesco Endoscopy

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**Core tip:** This systematic review demonstrates that the over-the-scope clip (OTSC) system is a safe and effective endoscopic therapy to manage gastrointestinal hemorrhage, perforations, anastomotic leaks, defects created by endoscopic resections and for stent fixation. Clinical success in fistula management appears limited. Further studies, including randomized controlled trials comparing OTSC with conventional and/or surgical therapies, are needed to determine which indication(s) are the most effective for its use.

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## INTRODUCTION

Acute (primary or refractory) gastrointestinal (GI) hemorrhage, perforation, GI fistulae, and anastomotic leaks are frequent occurrences in clinical GI practice that have been conventionally managed with surgery; however, the over-the-scope-clip (OTSC) system (Ovesco Endoscopy AG, Tübingen, Germany) has increasingly become an effective endoscopic treatment option in many cases as a primary and salvage treatment option, thereby decreasing the need for surgical intervention.

The OTSC system is a novel mechanical clipping device that allows for the endoscopic closure of large GI defects. It consists of an applicator cap, mounted clip, a hand wheel, thread, and thread retriever<sup>[1]</sup>. The clip is made of a super-elastic alloy (Nitinol), which is a biocompatible and magnetic resonance imaging conditional material (can be retained as a long-term implant)<sup>[1]</sup>. The applicator cap is available in a variety of sizes to accommodate endoscopes of different diameters (Table 1). The OTSC clips are offered in three different shapes (a, t, and gc) amenable to each indication: (1) Type “a” clips are blunted to provide compression of tissues and primarily used for hemostasis; (2) Type “t” clips have small spikes and blunted edges allowing for both compression and anchoring into tissues, and can be used for relatively thin walled portions of the GI tract such as the small intestine or colon; and (3) Type “gc” clips have elongated teeth (with spikes), which are primarily indicated for closure of gastric wall defects (Figure 1)<sup>[1]</sup>. Auxiliary accessories have recently become commercially available, including a clip designed for stent-fixation (Stentfix OTSC system; Ovesco Endoscopy AG, Tübingen, Germany), a smaller diameter applicator and clip for smaller lumens (mini OTSC; Ovesco Endoscopy AG, Tübingen, Germany), full thickness resection device (FTRD, Ovesco Endoscopy AG, Tübingen, Germany), and two forceps-like devices (OTSC Anchor, OTSC Twin Grasper; Ovesco Endoscopy AG, Tübingen, Germany). The Twin Grasper (TG) facilitates the approximation of gaping edges of a lesion prior to deployment of the OTSC clip (Figure 2), whereas the Anchor is able precisely align the target tissue and applicator cap, thus allowing for better approximation of tissue (especially when indurated)<sup>[1]</sup>.

The OTSC is delivered by means of an applicator cap mounted to the end of the endoscope using a thread retriever. If necessary, the TG or Anchor forceps may be used to allow for better approximation of the lesion. Turning the hand wheel attached

**Table 1** Over-the-scope clip types available for endoscope diameter and applicator clip depth<sup>2</sup>

OTSC cap options				
	Mini (10)	11	12	14
Scope outer diameter compatibility	8.5-9.8 mm	8.5-11 mm	10.5-12 mm	11.5-14 mm
	Diagnostic gastroscopes	Diagnostic gastroscopes	1T/2T gastroscopes, peds colonoscopes	Adult colonoscopes
Maximum outer diameter of cap	14.65 mm	16.5 mm	17.5 mm	21 mm
Thread length	165 cm	165 cm	165 cm or 220 cm	220 cm
Depth of applicator cap				
3 mm	a, t	a, t	a, t	a, t
6 mm	N/A	a, t	a, t, gc <sup>1</sup>	a, t

<sup>1</sup>Type “a” clips: Blunt teeth; Type “t”: Teeth with small spikes; Type “gc”: Teeth with elongated spikes (only available in size 12 cap); <sup>2</sup>Adapted from Over the scope clip System Brochure (Ovesco Endoscopy AG, Tübingen, Germany)<sup>[1]</sup>. N/A: Not applicable.

to the working channel of the endoscope allows for the thread connected to the applicator cap to tighten, thus deploying the clip to the targeted defect<sup>[1]</sup>. An additional clip may be used if a single clip does not sufficiently achieve adequate closure.

Kirschniak *et al*<sup>[2]</sup> first reported the clinical application of OTSC in 2007. The authors described seven refractory bleeding events, two iatrogenic perforations and two defects following endoscopic resection that were successfully managed with OTSC. A significant advantage of the OTSC system is the ability to achieve closure of luminal defects, or complex bleeding lesions with the deployment of a single clip, thus making its deployment more efficient than prior endoscopic strategies which utilized multiple through the scope (TTS) clips<sup>[3,4]</sup>. Prior to the availability of OTSC, complex luminal defects encountered during endoscopic procedures were often unable to be closed with conventional TTS clips due to lack of their ability to adequately approximate the defect margins, thus requiring surgical intervention in many instances. Furthermore, in the context of GI hemorrhage, the literature supports the use of OTSC when conventional endoscopic therapies fail<sup>[5,6]</sup>.

Advancements in therapeutic interventions across endoscopic practice currently facilitate larger and deeper resections of GI lesions, with a concurrent increase in iatrogenic injury<sup>[7-9]</sup>. OTSC has utility as a “real-time” intervention, allowing the endoscopist to effectively manage adverse events (AEs) quickly (such as bleeding and perforation) during the index procedure.

Since its inception, OTSC has become integrated into endoscopic practice internationally, with varying degrees of clinical success<sup>[10-12]</sup>. Though the OTSC system has been available for over ten years, it continues to benefit from iteration as further product development continues to take place. Data describing its use in the treatment of GI hemorrhage, perforation, anastomotic leaks, fistulae, defect closure after endoscopic resection and stent fixation is limited to primarily retrospective cohort studies and case series. Compiling and studying these published data in an organized manner would provide a more comprehensive understanding of the efficacy and safety profile of OTSC. This systematic review aims to determine the clinical success and AE rates of OTSC across various GI indications for use.

## MATERIALS AND METHODS

### Literature search strategy

This systematic review was performed according to the preferred reporting items for systematic reviews and meta-analysis statement<sup>[13]</sup>. A thorough search of the literature was conducted in the PubMed database to identify articles that described the use of OTSC for any GI indication from January 1, 2007 to January 15, 2020. The search was performed using the following terms: “over-the-scope-clip”, “OTSC”, “endoscopic fistula closure”, “over-the-scope clip bleeding”, “stent fixation”, and “endoscopic perforation closure.”

### Eligibility criteria

All English-language abstracts and/or full-text articles reporting original data of OTSC use (in humans, only) for the indication of fistulae, perforation, anastomotic leak closure, GI hemorrhage, endoscopic resection, and stent fixation were reviewed



**Figure 1** Over-the-scope clip types. A: Type "atraumatic"; B: Type "traumatic"; C: Type "gastric closure". Use of images with permission from Ovesco Endoscopy AG (Tübingen, Germany).

(authors: Bartell N and Bittner K) to assess eligibility for inclusion. Case reports and case series with fewer than five patients were excluded. Articles were also omitted if reported data did not include the rate of clinical success.

### Data extraction, outcomes and statistical analysis

Data extraction included the following: Author(s), year of publication, study type/design, location(s), number of patients, indication(s) for OTSC use, clinical and technical success rates (TSR), duration of follow-up, and OTSC-related AEs. The primary outcome of interest was clinical success rate (CSR). Secondary outcomes included TSR, requirement for surgical intervention despite OTSC, and reported OTSC-related AEs. Pooled rates (per-indication and overall) were calculated as the number of patients with the event of interest divided by the total number of patients.

### Definitions

CSR was defined as complete and durable resolution of the respective defect, hemorrhage and/or stent fixation. TSR was defined as the successful deployment of the OTSC clip to the targeted lesion or defect. OTSC-related AEs were defined as unanticipated events probably or possibly directly related to the use of the OTSC clip.

## RESULTS

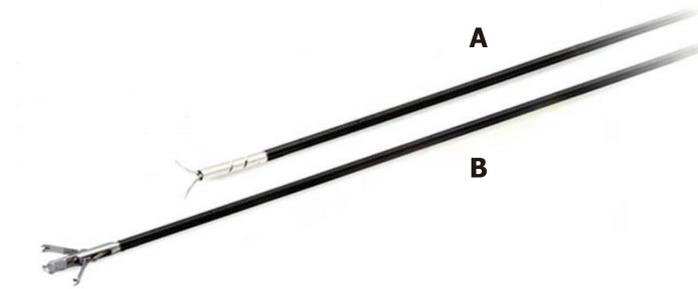
### Primary and secondary outcomes

A total of 512 record matches were located in the PubMed database, per the literature search strategy. Two authors (Bartell N and Bittner K) reviewed each title, abstract and/or full-text article prior to applying the full exclusion criteria. A total of 109 publications were retrieved for full review, with 24 excluded from the final analysis (Figure 3). Eighty-five articles<sup>[2-6,14-92]</sup> (Table 2) met inclusion criteria ( $n = 3025$  patients). Indications for OTSC use included: Fistulae ( $n = 622$ ), GI hemorrhage ( $n = 1303$ ), perforation ( $n = 468$ ), anastomotic leak closure ( $n = 391$ ), endoscopic resection defect closure ( $n = 221$ ), and stent fixation ( $n = 20$ ). The overall CSR (inclusive of all indications) and TSR for OTSC placement was 78.4% ( $n = 2371/3025$ ) and 94.4% ( $n = 2856/3025$ ), respectively. Per-indication CSR, TSR, and post-OTSC surgery rates are described in Table 3.

### GI hemorrhage

Endoscopic management of GI hemorrhage is well-established, with a number of available modalities to effectively achieve mechanical or coagulative hemostasis. Conventional endoscopic techniques are successful in managing GI hemorrhage in most cases; however, the rate of re-bleeding has been reported at 10%-20%<sup>[93]</sup>. Patients presenting with a re-bleed often require repeat endoscopic intervention, angiography (interventional radiology), or definitive management with surgery<sup>[93]</sup>. Mechanical hemostasis is often attempted with TTS clips which can be effective for smaller lesions; however, large and/or complex lesions may require a clip with larger diameter (up to 14 mm) and more tensile strength to achieve effective hemostasis.

In current endoscopic practice, OTSC is mainly used in refractory bleeding cases (Figure 4) following a failure of conventional therapy; however, a head-to-head randomized control trial (RCT) is currently being conducted in Europe (ClinicalTrials.gov, NCT03551262) to evaluate its efficacy as a potential primary therapy for hemostasis. Manno *et al*<sup>[44]</sup> retrospectively reviewed 40 consecutive cases of high-risk non-variceal upper GI hemorrhage utilizing OTSC as a primary



**Figure 2** Over the scope clip accessories. A: Over-the-scope clip Anchor; B: Over-the-scope clip Twin Grasper.

intervention. The authors reported a CSR of 100%, with no OTSC-related AEs (30-d follow up). In 2017, Wedi *et al*<sup>[74]</sup> highlighted the efficacy of OTSC in a retrospective review of 100 high-risk patients presenting with non-variceal upper GI bleeding. In this cohort, most (51%) of patients had severe cardiovascular comorbidities, with the majority (73%) on an antiplatelet regimen, thus potentially precluding a surgical approach in these patients. This article reported a CSR of 86% at 6 months of follow-up. In a subsequent study, Wedi *et al*<sup>[92]</sup> compared OTSC to standard of care treatment in non-variceal upper GI bleeding demonstrating superiority of OTSC, especially in high-risk patients. Specifically, patients with Rockall scores  $\geq 8$  showed significantly lower rates of re-bleeding when treated with OTSC as a first-line therapy as compared to patients treated with conventional modalities (10.9% *vs* 27.9%, respectively)<sup>[92]</sup>. Thus, OTSC can be used as the primary modality in high-risk patients such as those on anticoagulation, bleeding from large caliber vessels, or if they are not a good surgical candidate and/or as a rescue treatment for re-bleeding when conventional hemostasis options fail.

In our systematic review, the overall CSR and TSR for the indication of GI hemorrhage was 86.0% and 96.8%, respectively. Surgical intervention for control of GI hemorrhage following OTSC placement was only required in 1.6% (21/1303) of patients.

### Perforation

Though infrequent, perforation is an established risk of any endoscopic procedure, with average rates from 1 in 2500 to 1 in 11000 esophagogastroduodenoscopy's and 5.8 per 10000 for colonoscopy<sup>[94-96]</sup>. Advanced endoscopic interventions (including resection), have a higher risk of perforation than diagnostic procedures. Conventional management of acute iatrogenic perforation often necessitates surgical intervention; however, an effective and minimally invasive endoscopic approach to close these lesions during the index procedure is preferential to a higher-morbidity surgical intervention. Several endoscopic interventions have been utilized to manage perforations with varying degrees of success including: Self-expanding metal stents (SEMSs), TTS clips, endoscopic suturing, and OTSC<sup>[97]</sup>. SEMSs have been primarily used in the management of esophageal perforation; however, they carry the risk of migration and incomplete seal. TTS clips have limited ability to achieve complete closure of large defects and endoscopic suturing is limited by operator expertise, tedium and endoscope length in cases of perforation in the small bowel. Endoscopic suturing can also be challenging when managing defects in difficult locations such as gastric cardia, esophagus, duodenum, and proximal colon.

The European Society of GI Endoscopy currently recommends that endoscopic closure of iatrogenic perforations be considered during the index procedure<sup>[97]</sup>. OTSC is advantageous in this setting, as its ease of use, ability to close defects between 1-3 cm with a single clip application, and safety profile allow the endoscopist to effectively manage acute perforation immediately upon recognition (Figure 5)<sup>[97]</sup>. If the attempt to close perforation is delayed (> 72 h) or the defect is larger than 2 cm in diameter, endoscopic management is more likely to fail; however, the TG device can be utilized to approximate the edges of the defect for more effective closure with the OTSC, when dealing with larger defects (> 2 cm)<sup>[57,97]</sup>. Additionally, in cases of esophageal perforation, closure may be difficult with only suctioning the defect into the applicator cap (given the tangential orientation of the esophageal wall of to the endoscope). In this instance, the TG can help grasp the tissue to facilitate closure of the defect. Caution should be exercised while deploying the OTSC in difficult

**Table 2** Summary of included studies (overall clinical success rate, per-indication clinical success rate, and overall over-the-scope clip-related adverse event rate)

Ref.	Year	Type of study	Country	Patients (n)	Overall clinical success rate (%)						Follow-up (wk)	Adverse events, n (%)	
					Indications								
					Fistula	Bleeding	Perforation	Leak	ER	Stent fixation			
Seebach <i>et al</i> <sup>[15]</sup>	2010	Case series Retrospective	Switzerland	7	-	-	57.1	-	-	-	57.1	10-42	NR
Kirschniak <i>et al</i> <sup>[2]</sup>	2007	Retrospective	Germany	11	-	100	100	-	100	-	100	1-5	0.0
Mudumubi <i>et al</i> <sup>[16]</sup>	2014	Retrospective	International <sup>1</sup>	12	-	-	-	-	-	83.3	83.3	3-40	0.0
Sandmann <i>et al</i> <sup>[17]</sup>	2011	Case series Retrospective	Germany	11	100	-	100	66	100	-	90.9	12.7	NR
Albert <i>et al</i> <sup>[18]</sup>	2011	Retrospective	Germany	19	-	57.1	-	66.7	-	-	63.2	1-68	0.0
Repici <i>et al</i> <sup>[19]</sup>	2009	Case series Retrospective	Italy	9	-	100	-	-	100	-	100	4-12	0.0
Donatelli <i>et al</i> <sup>[20]</sup>	2016	Retrospective	International <sup>2</sup>	45	36.7	-	100	-	-	-	57.8	36-100	0.0
Mae-kawa <i>et al</i> <sup>[21]</sup>	2015	Prospective	Japan	12	-	-	-	-	91.7	-	91.7	NR	0.0
Gautier <i>et al</i> <sup>[22]</sup>	2015	Retrospective Multi-center	France	17	11.8	-	-	-	-	-	11.8	12	NR
Nishiyama <i>et al</i> <sup>[23]</sup>	2013	Retrospective	Japan	23	75	77.8	75	-	100	-	82.6	2-8	0.0
Voermans <i>et al</i> <sup>[24]</sup>	2012	Prospective Multi-center	Netherlands	36	-	-	88.9	-	-	-	88.9	1-26	0.0
Lee <i>et al</i> <sup>[26]</sup>	2017	Prospective Multi-center	Korea	19	25	-	100	83.3	100	-	73.7	72	0.0
Angsuwatharakon <i>et al</i> <sup>[27]</sup>	2016	Retrospective	Thailand	6	-	-	83.3	-	-	-	83.3	NR	NR
Arezzo <i>et al</i> <sup>[28]</sup>	2012	Case series prospective	Italy	14	-	-	-	85.7	-	-	85.7	16	0.0
Schlag <i>et al</i> <sup>[29]</sup>	2013	Prospective	Germany	6	-	-	100	-	-	-	100	4-12	0.0
Disibeyaz <i>et al</i> <sup>[30]</sup>	2012	Case series Retrospective	Turkey	9	33.3	-	100	60	-	-	55.6	NR	0.0
Gubler <i>et al</i> <sup>[31]</sup>	2012	Case series prospective	Switzerland	14	-	-	85.7	-	-	-	85.7	4-48	NR

Singhal <i>et al</i> <sup>[32]</sup>	2014	Case Series Prospective	United States	10	90	-	-	-	-	90	7	0.0	
Mennigen <i>et al</i> <sup>[33]</sup>	2013	Case series Retrospective	Germany	14	71.4	-	100	83.3	-	78.6	1-68	0.0	
Faehndrich <i>et al</i> <sup>[34]</sup>	2015	Retrospective	Germany	17	-	-	-	-	94.1	94.1	NR	0.0	
Schmidt <i>et al</i> <sup>[4]</sup>	2015	Prospective Multi-center RCT	International <sup>3</sup>	24	-	-	-	-	75	75	4	2 (8.3)	
Guo <i>et al</i> <sup>[35]</sup>	2015	Retrospective	China	23	-	-	-	-	100	100	4-24	2 (8.7)	
Correia <i>et al</i> <sup>[36]</sup>	2014	Case series prospective	Portugal	6	80	-	100	-	-	83.3	NR	0.0	
Goenka <i>et al</i> <sup>[37]</sup>	2017	Prospective	India	12	66	100	100	-	-	91.7	4-8	0.0	
Surace <i>et al</i> <sup>[38]</sup>	2011	Prospective	Italy	19	73.7	-	-	-	-	73.7	32	1 (5.3)	
Kochhar <i>et al</i> <sup>[39]</sup>	2017	Case series Prospective	United States	12	-	-	-	66.7	-	66.7	60	1 (8.3)	
Manta <i>et al</i> <sup>[40]</sup>	2017	Prospective	Italy	76	-	-	-	80.3	-	80.3	NR	0.0	
Parodi <i>et al</i> <sup>[41]</sup>	2010	Prospective	Italy	10	80	-	100	50	-	80.0	NR	0.0	
Manta <i>et al</i> <sup>[42]</sup>	2011	Case series Retrospective	Italy	12	87.5	-	-	75	-	83.3	4	0.0	
Honegger <i>et al</i> <sup>[43]</sup>	2017	Retrospective Cohort	Switzerland	203	29.8	77.4	86.1	33.3	-	66.7	63.1	4	6 (3.0)
Manno <i>et al</i> <sup>[44]</sup>	2015	Retrospective	International <sup>4</sup>	40	-	100	-	-	-	100	4	0.0	
Richter-Schrag <i>et al</i> <sup>[45]</sup>	2016	Retrospective	Germany	100	-	78	-	-	-	78	NR	NR	
Aepli <i>et al</i> <sup>[46]</sup>	2016	Retrospective	Switzerland	24	-	-	-	-	87.5	87.5	NR	4 (16.7)	
Law <i>et al</i> <sup>[48]</sup>	2015	Retrospective Multi-center	United States	47	53.2	-	-	-	-	53.2	26	0.0	
Farnik <i>et al</i> <sup>[5]</sup>	2015	Retrospective Multi-center	International <sup>5</sup>	34	-	-	100	56.3	-	70.5	39	0.0	
Jacobsen <i>et al</i> <sup>[49]</sup>	2012	Retrospective	United States	10	0	-	100	80	-	70.0	12	0.0	
Haito-Chavez <i>et al</i> <sup>[50]</sup>	2014	Retrospective Multi-center	International <sup>6</sup>	161	42.9	-	90	73.3	-	60.2	18 – 30	0.0	
Winder <i>et al</i> <sup>[51]</sup>	2016	Retrospective	United States	28	77.2	-	-	100	-	82.1	19	0.0	
Sulz <i>et al</i> <sup>[52]</sup>	2014	Case series prospective	Switzerland	19	54.5	100	-	66.7	-	100	63.1	NR	0.0

Magdeburg <i>et al</i> <sup>[53]</sup>	2015	Prospective	Germany	43	-	-	97.8	-	-	-	97.8	NR	3 (7.0)
Wedi <i>et al</i> <sup>[54]</sup>	2016	Retrospective	France	84	100	89.3	57.1	-	100	-	89.3	NR	2 (2.4)
Keren <i>et al</i> <sup>[55]</sup>	2014	Case series prospective	Israel	26	-	-	-	80.8	-	-	80.8	NR	0.0
Raithel <i>et al</i> <sup>[14]</sup>	2017	Retrospective Multi-center	Germany	34	-	-	74.1	85.7	-	-	76.5	NR	3 (8.8)
Kobara <i>et al</i> <sup>[56]</sup>	2017	Retrospective Multi-center	Japan	58	83.3	83.3	-	85.7	-	-	84.5	4+	1 (1.8)
Hagel <i>et al</i> <sup>[57]</sup>	2012	Case series prospective	Germany	17	-	-	64.7	-	-	-	64.7	4	NR
Nasa <i>et al</i> <sup>[58]</sup>	2016	Case series retrospective	India	7	80	100	100	-	-	-	85.7	45	NR
Skinner <i>et al</i> <sup>[6]</sup>	2014	Retrospective	United States	12	-	83.3	-	-	-	-	83.3	10 – 30	0.0
Al-Bawardiy <i>et al</i> <sup>[59]</sup>	2017	Retrospective	United States	7	-	-	-	-	100	-	100	1 – 86	0.0
Sarker <i>et al</i> <sup>[60]</sup>	2014	Retrospective	United States	8	-	-	-	-	100	-	100	4 – 52	0.0
Man-giavillano <i>et al</i> <sup>[61]</sup>	2016	Retrospective	Italy	20	-	-	90	-	-	-	90	12	NR
Aiolfi <i>et al</i> <sup>[62]</sup>	2014	Retrospective	Italy	7	-	-	-	85.7	-	-	85.7	NR	NR
Manta <i>et al</i> <sup>[5]</sup>	2013	Case series Multi-center	Italy	30	-	90	-	-	-	-	90	1 – 4	0.0
Man-giastico <i>et al</i> <sup>[63]</sup>	2017	Case series prospective	International <sup>7</sup>	7	100	-	-	-	-	-	100	2 – 8	0.0
Niland <i>et al</i> <sup>[64]</sup>	2017	Retrospective	United States	14	21.4	-	-	-	-	-	21.4	26	0.0
Schmdtt <i>et al</i> <sup>[4]</sup>	2018	Prospective RCT	International <sup>8</sup>	33	-	84.8	-	-	-	-	84.8	4	0.0
Heinrich <i>et al</i> <sup>[65]</sup>	2017	Case series retrospective	Switzerland	5	100	-	-	-	-	-	100	46 – 269	0.0
Prosst <i>et al</i> <sup>[66]</sup>	2015	Prospective	Germany	20	90	-	-	-	-	-	90	24	0.0
Mizrahi <i>et al</i> <sup>[67]</sup>	2016	Prospective	United States	51	35.3	75	75	50	-	50	49.0	48	NR
Kirschniak <i>et al</i> <sup>[68]</sup>	2011	Retrospective	Germany	46	37.5	93	100	-	-	-	84.8	1 – 2	0.0
Mennigen <i>et al</i> <sup>[69]</sup>	2015	Retrospective	Germany	10	70	-	-	-	-	-	70	22 – 75	0.0
Wedi <i>et al</i> <sup>[70]</sup>	2016	Retrospective Case series	International <sup>9</sup>	6	-	100	-	-	-	-	100	NR	NR

Baron <i>et al</i> <sup>[71]</sup>	2012	Retrospective Multi-center	United States	43	67.9	100	80	33.3	-	-	72.1	4 - 11	2 (4.7)
Lamberts <i>et al</i> <sup>[72]</sup>	2017	Retrospective	Germany	75	-	65.3	-	-	-	-	65.3	NR	NR
Soetikno <i>et al</i> <sup>[73]</sup>	2016	Case series retrospective	International <sup>10</sup>	5	-	100	-	-	-	-	100	60	0.0
Wedi <i>et al</i> <sup>[74]</sup>	2017	Retrospective	International <sup>11</sup>	100	-	86	-	-	-	-	73	NR	NR
Chan <i>et al</i> <sup>[75]</sup>	2014	Case series prospective	China	9	-	77.8	-	-	-	-	77.8	8	NR
Keen <i>et al</i> <sup>[76]</sup>	2019	Prospective	United Kingdom	59	-	93.2	-	-	-	-	93.2	4	NR
Horenkamp-Sonntag <i>et al</i> <sup>[77]</sup>	2019	Retrospective	Germany	92	-	82.4	87.9	-	-	-	92.4	14	NR
Manta <i>et al</i> <sup>[78]</sup>	2019	Retrospective Multi-center	Italy	286	-	94.4	-	-	-	-	94.4	4	NR
Mercky <i>et al</i> <sup>[79]</sup>	2015	Retrospective	France	30	73.3	-	-	-	-	-	73.3	42	3 (10)
Monkemuller <i>et al</i> <sup>[80]</sup>	2014	Case series retrospective	Germany	16	50	100	-	0	100	100	75	44	0.0
Bonino <i>et al</i> <sup>[81]</sup>	2014	Case series prospective	Italy	26	90	-	68.8	-	-	-	76.9	NR	0.0
Christophorou <i>et al</i> <sup>[82]</sup>	2015	Retrospective Multi-center	France	14	78.5	-	-	-	-	-	78.5	NR	NR
Lunse <i>et al</i> <sup>[83]</sup>	2019	Retrospective	Germany	9	66.7	-	-	-	-	-	66.7	8	0.0
Mosquera-Klinger <i>et al</i> <sup>[84]</sup>	2019	Retrospective Case series	Columbia	14	70	100	100	-	-	100	78.6	20	0.0
Brander <i>et al</i> <sup>[25]</sup>	2017	Retrospective	United States	67	-	70.1	-	-	-	-	70.1	4	NR
Meier <i>et al</i> <sup>[47]</sup>	2017	Retrospective	Germany	10	-	-	-	-	100	-	100	12	0.0
Tashima <i>et al</i> <sup>[85]</sup>	2017	Prospective	Japan	50	-	-	-	-	94	-	94	2	4 (8)
Khater <i>et al</i> <sup>[86]</sup>	2017	Retrospective	France	11	-	-	81.2	-	-	-	81.2	NR	1 (9)
Asokkumar <i>et al</i> <sup>[87]</sup>	2018	Retrospective	International <sup>12</sup>	19	-	100	-	-	-	-	100	NR	0.0
Morrell <i>et al</i> <sup>[88]</sup>	2019	Retrospective	United States	117	50.8	-	-	75	-	-	61.2	22	0.0
Kappelle <i>et al</i> <sup>[89]</sup>	2018	Prospective	Netherlands	13	-	-	-	-	84.6	-	84.6	24	5 (38.4)
Wei <i>et al</i> <sup>[90]</sup>	2019	Retrospective	China	26	-	-	100	-	-	-	100	4	0.0
Golder <i>et al</i> <sup>[91]</sup>	2019	Retrospective	Germany	100	-	75	-	-	-	-	75	NR	0.0

Wedi <i>et al</i> <sup>[92]</sup>	2018	Retrospective Multi-center	Germany	118	-	92.4	-	-	-	-	92.4	4	NR
Total				3025	55.8%	86.0%	85.3%	72.6%	92.8%	80.0%	78.4%	-	2.1%
					347/622	1120/1303	399/468	284/391	205/221	16/20	2371/3025	-	40/1942 <sup>13</sup>

<sup>1</sup>Germany, United States.

<sup>2</sup>France, Italy, India.

<sup>3</sup>Switzerland, Germany.

<sup>4</sup>Italy, United Kingdom.

<sup>5</sup>Germany, Japan.

<sup>6</sup>United States, Italy, Germany, Netherlands, Chile.

<sup>7</sup>Italy, United Kingdom.

<sup>8</sup>Germany, China, Switzerland.

<sup>9</sup>Germany, France, Canada, United States.

<sup>10</sup>United States, Singapore.

<sup>11</sup>Germany, France, Canada, United States.

<sup>12</sup>Singapore, Spain.

<sup>13</sup>Over the scope clip-related adverse events were only reported for 1958 of 3041 patients ( $n = 65$  studies). NR: Not reported; ER: Endoscopic resection; RCT: Randomized control trial.

locations (*e.g.*, gastro-esophageal junction, pylorus and the duodenal sweep) to avoid closing off the lumen entirely.

Honegger *et al*<sup>[43]</sup> reported on the efficacy of OTSC in a large cohort of patients ( $n = 72$ ) with iatrogenic endoscopic perforations, with a stated CSR of 86.1%. Two patients experienced OTSC-related AEs, with one case of bleeding and one with a worsening of the index perforation. In a recent study, Wei *et al*<sup>[90]</sup> described the use of OTSC in patients with perforated peptic ulcer compared to a control group that was managed conventionally. The rate of clinical success in the OTSC group was 100% ( $n = 26/26$ ) *vs* only 57.5% ( $n = 46/80$ ) in controls. The requirement for surgical intervention in the OTSC cohort was significantly lower than controls (0% *vs* 30.0%, respectively,  $P < 0.001$ ). No OTSC-related AEs were reported<sup>[90]</sup>.

In our systematic review the overall CSR and TSR for the indication of perforation was 85.3% and 95.5%, respectively. Surgical intervention post-OTSC placement was required to achieve complete closure in 9.4% ( $n = 44/468$ ) of patients.

### Defect closure following endoscopic resection

Prior to the availability of OTSC, prophylactic closure of defects created by endoscopic resection of GI lesions would be managed with TTS clips. Prophylactic TTS clip closure following the resection of large (> 1 cm) proximal colonic lesions is an effective strategy that has reduced the incidence of post-procedure AEs (including post-polypectomy hemorrhage) and increased patient satisfaction<sup>[98-100]</sup>; however, TTS are limited by their diameter and often require a “suturing” technique involving the placement of multiple clips across the lesion. With the deployment of OTSC, a defect of 1-3 cm in diameter can be successfully closed utilizing a single clip<sup>[98]</sup>.

The full-thickness resection device (FTRD; Ovesco Endoscopy AG, Tübingen, Germany) is now commercially available. This accessory combines the ability to complete resection and clipping with a single device. Aepli *et al*<sup>[46]</sup> reported the first clinical data in 2016 on the use of FTRD, demonstrating a CSR ( $n = 24$  patients) of 87.5% and a post-OTSC AE rate of 12.5% ( $n = 4/24$ ) with 3 post-procedure bleeding events and one post procedure perforation.

In our systematic review the overall CSR and TSR for the indication of defect closure following endoscopic resection was 92.8% and 95.9%, respectively. The necessity for post-OTSC surgical intervention was rare ( $n = 2/221$ ; 0.9%).

### Fistula closure

GI fistulae are difficult to manage with either endoscopic or surgical interventions, likely due to the chronicity of the problem, fibrotic non healing tracts and prior treatment attempts making subsequent closure increasingly difficult. In addition, the underlying pathogenesis combined with a presentation of impaired nutritional status contribute to slow or non-healing of the fistula. Conventional management of GI fistulae focuses on control/prevention of infection, optimization of nutrition/hydration, and limiting of fistula output. Surgical management can be attempted as a definitive therapy in lower-risk patients; however, patients with complex fistulae may be too medically frail for surgical intervention and/or those presenting with a small bowel fistula may not have enough remnant bowel to allow for further resection.

In recent years, endoscopy been considered as a possible primary therapy for the

**Table 3 Over-the-scope clip-related adverse events, per-indication**

	Incorrect placement site	Perforation	Bleeding	Infection	Overall
Fistula	0	3	0	2	5
Bleeding	0	0	0	0	0
Perforation	2	2 <sup>2</sup>	2	1	7
Leak	1	1	0	1	3
ER	4	2	7	6	19
Stent fixation	0	0	0	0	0
Total	7	8	9	10	34 <sup>1</sup>

<sup>1</sup>The total number of Over the scope clip-related adverse events recorded was 40; however, one article (Honegger *et al.*<sup>[41]</sup>) did not report adverse events per-indication and thus cannot be included in this table. A total of six such events occurred, including: incorrect placement site ( $n = 4$ ), perforation ( $n = 1$ ) and bleeding ( $n = 1$ );

<sup>2</sup>Adverse events for the initial indication of perforation are defined as exacerbation or worsening of the index perforation qualifying as a separate adverse event. ER: Endoscopic resection.

closure of GI fistulae<sup>[101]</sup>. Prior to the advent of OTSC, endoscopic treatment of GI fistulae had been attempted with TTS, absorbable loop snares or glues to varying degrees of success<sup>[102]</sup>. OTSC has potential in the management of GI fistulae (Figure 6), as the suction utilized in the clip application can create a more robust closure than TTS; however, definitive closure of a fistula relies on the complete grasping of involved tissue within the clipping device, which may be difficult when fibrotic tissue is present, as in most fistulae. High rates of clinical success for fistula closure have not yet been reported with OTSC. Haito-Chavez *et al.*<sup>[50]</sup> reported the largest study of OTSC use in patients with fistulae ( $n = 91$  patients) secondary to percutaneous endoscopic gastrostomy or jejunostomy tubes, post-bariatric surgery, malignancy-related, trauma, inflammatory bowel disease or diverticulitis. Deployment of the OTSC was successful in 89.4% of patients; however, clinical success at a median of 121 d was only 42.9%<sup>[50]</sup>. Other studies have reported similar CSR for fistula closure with OTSC<sup>[48]</sup>. Haito-Chavez *et al.*<sup>[50]</sup> discuss the likelihood that fistulae with fibrotic and retracted rims were most associated with clinical failure, possibly related to the difficulty in properly targeting and suctioning the tissue during OTSC application. Fistulae smaller than 1 cm could be considered for closure with OTSC; however, in cases with a large fistula ( $> 1$  cm) more than one clip could be applied and/or utilized in combination with endoscopic suturing with reinforced OTSC or glue to successfully achieve closure.

In our systematic review the overall CSR and TSR for the indication of fistulae was 55.8% and 92.8%, respectively. Surgical intervention post-OTSC placement was required in 7.6% ( $n = 47/622$ ) of patients.

### Closure of anastomotic leaks

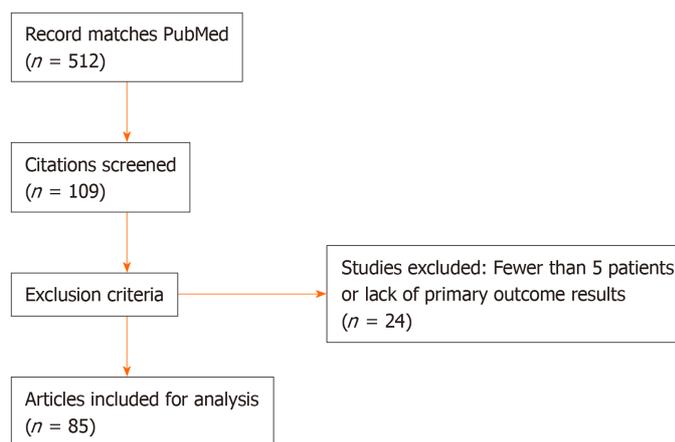
Conventional management for anastomotic leaks often follows a conservative approach of broad-spectrum antibiotics for lower-risk lesions and/or repeated surgical intervention for higher-risk lesions. The probability of a post-surgical anastomotic leak is higher in patients with a low serum albumin, longer operative time, higher intraoperative blood loss, positive resection margins or the presence of inflammatory bowel disease<sup>[103]</sup>. An effective minimally invasive endoscopic approach is preferable, as many of these patients may be too high-risk for additional surgical intervention.

Manta *et al.*<sup>[42]</sup> presented the largest case series of patients ( $n = 76$ ) with anastomotic leaks included in this review. Post-surgical leaks appeared in both the upper ( $n = 47$ ) and lower ( $n = 29$ ) GI tract. Overall clinical success was achieved in 80.3% of patients (83% and 75.9% for upper and lower GI leaks, respectively)<sup>[42]</sup>.

In our systematic review the overall CSR and TSR for the indication of anastomotic leak closure was 72.6% and 86.7%, respectively. Surgical intervention post-OTSC placement was required in 7.4% (29/391) of patients.

### Stent fixation

GI stenting (most often for tumor palliation) though effective in immediate symptomatic relief, is often plagued by stent migration, especially in the case of fully covered stents<sup>[104]</sup>. The availability of SEMs has reduced the risk of migration; however, the potential still exists<sup>[105]</sup>. OTSC can be used to anchor SEMs to mitigate the risk of stent migration. Limited data exist on the application of OTSC in this



**Figure 3** Article selection process, per preferred reporting items for systematic reviews and meta-analysis guideline.

setting. The largest paper in the literature was presented by Mudumbi *et al*<sup>[16]</sup>, demonstrating a high CSR (83%) in 12 patients who underwent OTSC fixation of SEMS, with no reported OTSC-related AEs. If it is necessary to remove a stent anchored by OTSC, the clip itself will need to be detached to do so, which is neither easy nor predictable. Traditionally, the only feasible method to remove the OTSC was with argon plasma coagulation; however, a novel device (remOVE system; Ovesco Endoscopy AG, Tübingen, Germany) has since been developed to effectively detach the OTSC<sup>[106,107]</sup>.

In our systematic review the overall CSR and TSR for the indication of stent fixation was 80.0% and 100%, respectively; however, only 20 patients were included due to the paucity of data regarding OTSC for stent fixation in the literature. No patients required surgical intervention following OTSC placement or as a result of removal.

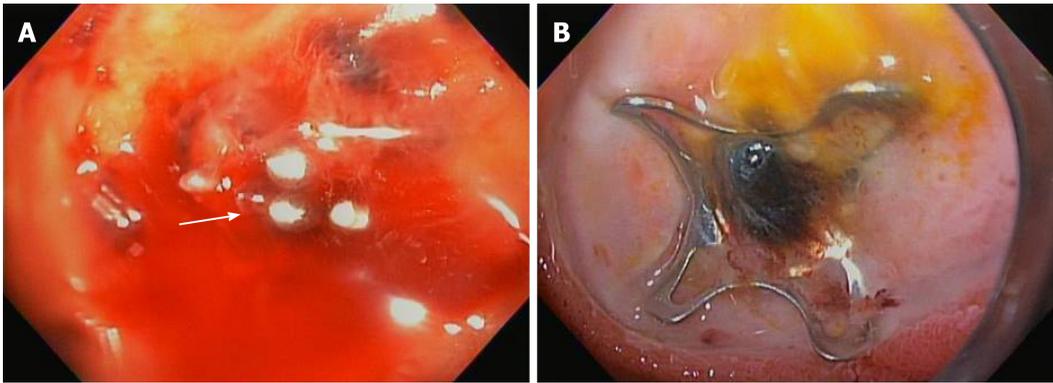
### OTSC-related AEs

Sixty-four studies ( $n = 1942$  patients) reported OTSC-related AE data (Table 4), with an overall rate of 2.1% ( $n = 40/1,942$ ). These events included: “incorrect placement site” ( $n = 11/40$ ; 27.5%), perforation ( $n = 9/40$ ; 22.5%), bleeding ( $n = 10/40$ ; 25%), and infection ( $n = 10/40$ ; 25%). No deaths occurred as a result of OTSC use.

A perforation was defined as an AE if the OTSC: (1) Caused a de novo perforation, or (2) Worsened an already existing perforation that the OTSC was intended to close. “Incorrect placement site” was defined as the placement of the OTSC in a location other than the targeted defect and/or the disruption of nearby tissue/structures by the OTSC. For instance, Honegger *et al*<sup>[43]</sup> reported three cases of inadvertent OTSC deployment on the tongue during withdrawal of the endoscope and one case of OTSC deployment in the rectum causing a pseudopolyp formation resulting in a clinically significant obstruction. Raithel *et al*<sup>[14]</sup> reported a case of colonic perforation managed with OTSC resulting in fixation of the small bowel to the colon and subsequent rupture of the small bowel requiring surgical intervention. Khater *et al*<sup>[86]</sup> further described the potential of the OTSC to disrupt nearby tissue/structures reporting a case of rectosigmoid perforation that was effectively closed with OTSC; however, follow-up imaging studies demonstrated dilation of the urinary tract and ureter obstruction as a result of the ureter being suctioned into the application cap during clip deployment. Ultimately this patient required surgical intervention<sup>[86]</sup>. Such cases highlight the potential hazards and drawbacks related to the application of the OTSC clip, therefore careful consideration of surrounding anatomy should be entertained prior to OTSC deployment. Though the incorrect placement of OTSC can be a significant AE (due to difficulty in OTSC removal), the remOVE device is now available to detach the OTSC if placement of the clip is not satisfactory. Preliminary data suggest successful fragmentation of the OTSC with remOVE in 97.3% of cases, with minimal AEs (bleeding in 2.7% of patients, and superficial mucosal tearing in 1.4% of patients)<sup>[107]</sup>.

## DISCUSSION

To our knowledge, this systematic review represents the most comprehensive data (3025 cases over a period of 12 years; 2007-2019) of OTSC use across all GI indications.



**Figure 4** Over the scope clip used in management of gastrointestinal bleeding. A: Massive gastrointestinal bleeding from duodenal bulb ulcer with an actively bleeding blood vessel; B: Successful hemostasis achieved using over-the-scope-clip.

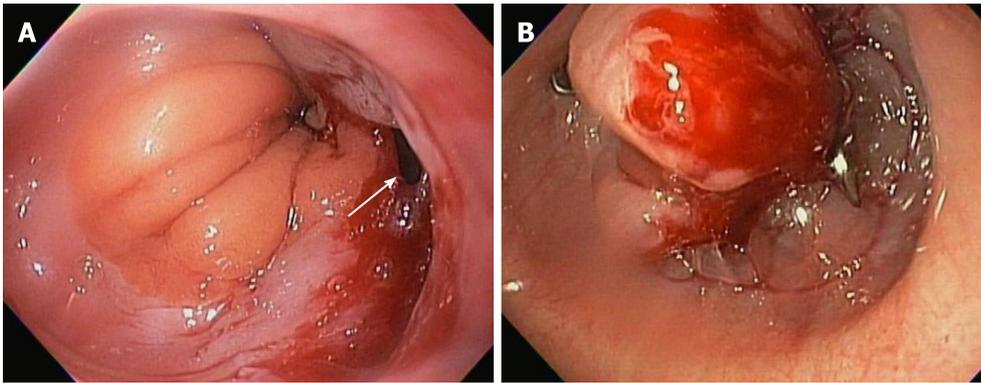
A high CSR (> 75%) was reported in the majority of clinical applications of OTSC. Our review confirms the efficacy of OTSC in preventing surgical intervention in most cases, as only 4.7% ( $n = 143/3025$ ) of patients required salvage surgery, despite OTSC placement. OTSC can be considered for patients that are too high-risk for surgery but who can still tolerate endoscopy. OTSC facilitates effective endoscopic management of iatrogenic complications and known complex defects that previously may have only been amenable to surgical repair.

When each indication for OTSC placement is evaluated individually, there are clear disparities in CSRs for certain indications. A CSR of greater than 85% was observed in the management of GI hemorrhage, perforation and defect closure following endoscopic resection with OTSC; however, fistula closure was comparatively much less successful with a CSR of 55.8%. The lower efficacy of OTSC in fistula closure compared to other indications is thought to be multifactorial from the chronicity of the underlying problem and other variables discussed above that can make subsequent closure attempts challenging. Further innovation in technology and accessories can help close this gap in effectiveness across various indications and improve the effectiveness of OTSC in challenging scenarios.

In one of the earlier published articles on OTSC, Seebach *et al*<sup>[15]</sup> noted that OTSC has the potential to “spare the surgeon”. Our review strengthens this opinion as there was no indication for OTSC placement in which a rate of post-OTSC surgery was greater than 10%. Prior to the use of OTSC, surgical intervention would have been required for most of the patients included in this review. The rates of surgery, and the AEs, morbidity and mortality associated with it, will decrease for patients as OTSC becomes more integrated into routine endoscopic practices. Furthermore, patients who previously were deemed to be poor surgical candidates may now be able to be successfully managed with a less invasive and effective endoscopic approach.

The main limitation of this review is the level of available evidence related to OTSC use, as there is a paucity of RCTs or large multi-center analyses in the literature. The majority of articles include a relatively small sample size and/or are a summation of a single-center’s experience with OTSC use across multiple indications. In addition, our review lacks a large cohort of patients that underwent OTSC placement following endoscopic resection or for stent fixation. The potential for selection bias in pooling results from case series or single-center retrospective studies is acknowledged. Case series are often likely to underrepresent AEs and negative outcomes, as often authors are interested in adding positive results to the literature. Our review attempted to limit this bias by including studies with five or more patients. When isolating studies with a prospective design only (Table 5), a similar overall CSR and OTSC-related AE rate was demonstrated, suggesting that pooled retrospective data may be truly representative of the efficacy and safety of OTSC. The potential for lack of generalizability to a community setting may exist due to the likelihood that the majority of endoscopists currently utilizing OTSC in their practice are considered “experts” and/or performing some level of advanced endoscopic procedures.

In conclusion, it is clear that the OTSC device represents a major advance in endoscopic practice and has enabled a “paradigm shift” in how we manage a variety of endoscopic challenges today. Our systematic review demonstrates that the OTSC system is a safe and effective endoscopic therapy to manage GI hemorrhage, perforation, anastomotic leaks, defects created by endoscopic resection, and for stent fixation; however, success in fistulae was limited. Further studies, including randomized controlled trials comparing OTSC with conventional and/or surgical



**Figure 5** Over the scope clip used in management of gastrointestinal perforation. A: Gastro-esophageal junction perforation caused during advancement of side viewing duodenoscope; B: Successful closure of perforation using over-the-scope-clip.

therapies, are needed to determine which indication(s) are the most appropriate for its use and also to clarify the true AE rate, need for surgical salvage and any other technical aspects of OTSC use that may further clarify the role of OTSC in current and future endoscopic practice.

**Table 4** Per-indication clinical success rate, technical success rate, and post-over-the-scope clip surgery rates

	Clinical success rate (%), (n/N)	Technical success rate (%), (n/N)	Post-over the scope clip surgical rate (%), (n/N)
Fistula	55.8 (347/622)	92.8 (577/622)	7.6 (47/622)
Bleeding	86.0 (1120/1303)	96.8 (1261/1303)	1.6 (21/1303)
Perforation	85.3 (399/468)	95.5 (447/468)	9.4 (44/468)
Leak	72.6 (284/391)	86.7 (339/391)	7.4 (29/391)
ER	92.8 (205/221)	95.9 (212/221)	0.9 (2/221)
Stent fixation	80.0 (16/20)	100 (20/20)	0.0 (0/20)
Overall	78.4 (2371/3025)	94.4 (2856/3025)	4.7 (143/3025)

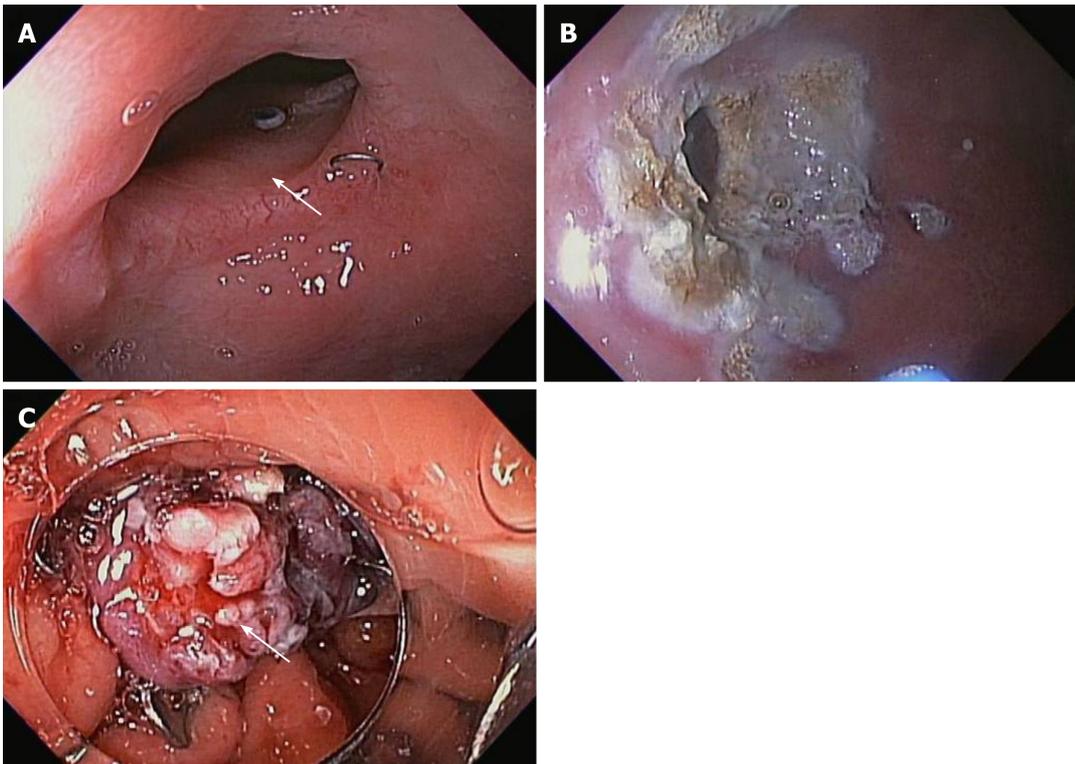
ER: Endoscopic resection.

**Table 5** Summary of prospective studies (overall clinical success rate, per-indication clinical success rate and adverse event rate)

Ref.	Year	Type of study	Country	Patients (n)	Overall clinical success rate (%)							Follow-up (wk)	Adverse events, n (%)
					Indications						Total		
					Fistula	Bleeding	Perforation	Leak	ER <sup>3</sup>	Stent fixation			
Mae-kawa <i>et al</i> <sup>[21]</sup>	2015	Prospective	Japan	12	-	-	-	-	11/12	-	11/12	NR	0.0
Voermans <i>et al</i> <sup>[24]</sup>	2012	Prospective Multi-center	Netherlands	36	-	-	32/36	-	-	-	32/26	1-26	0.0
Lee <i>et al</i> <sup>[26]</sup>	2017	Prospective Multi-center	Korea	19	1/4	-	1/1	10/12	1/2	-	13/19	72	0.0
Arezzo <i>et al</i> <sup>[28]</sup>	2012	Case series prospective	Italy	14	-	-	-	12/14	-	-	12/14	16	0.0
Schlag <i>et al</i> <sup>[29]</sup>	2013	Prospective	Germany	6	-	-	6/6	-	-	-	6/6	4-12	0.0
Gubler <i>et al</i> <sup>[31]</sup>	2012	Case series prospective	Switzerland	14	-	-	12/14	-	-	-	12/14	4-48	NR
Singhal <i>et al</i> <sup>[32]</sup>	2014	Case series prospective	United States	10	9/10	-	-	-	-	-	9/10	7	0.0
Schmidt <i>et al</i> <sup>[4]</sup>	2015	Prospective Multi-center RCT	International <sup>1</sup>	24	-	-	-	-	18/24	-	18/24	4	2 (8.3)
Correia <i>et al</i> <sup>[36]</sup>	2014	Case series prospective	Portugal	6	4/5	-	1/1	-	-	-	5/6	NR	0.0
Goenka <i>et al</i> <sup>[37]</sup>	2017	Prospective	India	12	2/3	6/6	3/3	-	-	-	11/12	4-8	0.0
Surace <i>et al</i> <sup>[38]</sup>	2011	Prospective	Italy	19	14/19	-	-	-	-	-	14/19	32	1 (5.3)
Kochhar <i>et al</i> <sup>[39]</sup>	2017	Case series prospective	United States	12	-	-	-	8/12	-	-	8/12	60	1 (8.3)
Manta <i>et al</i> <sup>[40]</sup>	2017	Prospective	Italy	76	-	-	-	61/76	-	-	61/76	NR	0.0

Parodi <i>et al</i> <sup>[41]</sup>	2010	Prospective	Italy	10	4/5	-	3/3	1/2	-	-	8/10	NR	0.0
Sulz <i>et al</i> <sup>[52]</sup>	2014	Case series prospective	Switzerland	19	6/11	1/1	-	4/6	-	1/1	12/19	NR	0.0
Magdeburg <i>et al</i> <sup>[53]</sup>	2015	Prospective	Germany	43	-	-	42/43	-	-	-	42/43	NR	3 (7.0)
Keren <i>et al</i> <sup>[55]</sup>	2014	Case series prospective	Israel	26	-	-	-	21/26	-	-	21/26	NR	0.0
Hagel <i>et al</i> <sup>[57]</sup>	2012	Case series prospective	Germany	17	-	-	11/17	-	-	-	11/17	4	NR
Mangiafico <i>et al</i> <sup>[63]</sup>	2017	Case series prospective	International <sup>2</sup>	7	7/7	-	-	-	-	-	7/7	2-8	0.0
Schmdtt <i>et al</i> <sup>[4]</sup>	2018	Prospective RCT	International <sup>3</sup>	33	-	28/33	-	-	-	-	28/33	4	0.0
Prosst <i>et al</i> <sup>[66]</sup>	2015	Prospective	Germany	20	18/20	-	-	-	-	-	18/20	24	0.0
Mizrahi <i>et al</i> <sup>[67]</sup>	2016	Prospective	United States	51	6/17	3/4	3/4	12/24	-	1/2	25/51	48	NR
Chan <i>et al</i> <sup>[75]</sup>	2014	Case series prospective	China	9	-	7/9	-	-	-	-	7/9	8	NR
Keen <i>et al</i> <sup>[76]</sup>	2019	Prospective	United Kingdom	59	-	55/59	-	-	-	-	55/59	4	NR
Tashima <i>et al</i> <sup>[85]</sup>	2017	Prospective	Japan	50	-	-	-	-	47/50	-	47/50	2	4 (8)
Kapelle <i>et al</i> <sup>[89]</sup>	2018	Prospective	Netherlands	13	-	-	-	-	11/13	-	11/13	24	5 (38.4)
Total				617	70.3%	89.3%	89.1%	75.0%	87.1%	66.7%	81.7%	-	3.4%
					71/101	100/112	114/128	129/172	88/101	2/3	504/617	-	16/467 <sup>4</sup>

<sup>1</sup>Switzerland, Germany.<sup>2</sup>Italy, United Kingdom.<sup>3</sup>Germany, China, Switzerland.<sup>4</sup>Over the scope clip-related adverse events were only reported for 467 of 617 patients ( $n = 21$  studies). NR: Not reported; ER: Endoscopic resection; RCT: Randomized control trial.



**Figure 6** Over the scope clip used in management of gastrointestinal fistula. A: Gastro-gastric fistula in a patient with Roux-en-Y gastric bypass; B: Argon plasma coagulation ablation of the fistula margin; C: Successful closure of fistula using over-the-scope-clip.

## ARTICLE HIGHLIGHTS

### Research background

The over-the-scope-clip (OTSC) device has become widely utilized in endoscopic practice. Limited data exist evaluating the overall clinical success and adverse event (AE) rates of OTSC across gastrointestinal (GI) indications.

### Research motivation

The key significance of this systematic review is to provide endoscopists with a real-world estimate of the efficacy and safety of OTSC in clinical practice.

### Research objectives

The aim of this study was to determine the rates of clinical success (CSR), technical success (TSR), AE and post-OTSC (salvage) surgery rates.

### Research methods

A PubMed search was conducted for eligible articles describing the use of OTSC for any GI indication. Any article or case series reporting data for less than 5 total patients was excluded. Articles were included from January 1, 2007 to January 15, 2020. The following terms were used to perform the literature search: "over-the-scope-clip", "OTSC", "endoscopic fistula closure," "over-the-scope clip bleeding", "stent fixation", and "endoscopic perforation closure."

### Research results

Eighty-five articles met inclusion criteria ( $n = 3025$  patients). The overall CSR (inclusive of all indications) and TSR for OTSC placement was 78.4% ( $n = 2371/3025$ ) and 94.4% ( $n = 2856/3025$ ), respectively.

### Research conclusions

OTSCs are a novel advancement in endoscopic practice. They are safe and effective for use in GI hemorrhage, anastomotic leak, perforation, defects created by endoscopic resection and stent fixation; however, there is room for improvement in use for fistula closure.

### Research perspectives

Future large randomized control trials comparing OTSC with conventional and/or surgical interventions are needed to develop clinical guidelines for the most appropriate endoscopic application(s).

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