Efficacy and safety of over-the-scope clip: Including complications after endoscopic submucosal dissection

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Abstract

AIM: To retrospectively review the results of over-the-scope clip (OTSC) use in our hospital and to examine the feasibility of using the OTSC to treat perforations after endoscopic submucosal dissection (ESD).

METHODS: We enrolled 23 patients who presented with gastrointestinal (GI) bleeding, fistulae and perforations and were treated with OTSCs (Ovesco Endoscopy GmbH, Tuebingen, Germany) between November 2011 and September 2012. Maximum lesion size was defined as lesion diameter. The number of OTSCs to be used per patient was not decided until the lesion was completely closed. We used a twin grasper (Ovesco Endoscopy GmbH, Tuebingen, Germany) as a grasping device for all the patients. A 9 mm OTSC was chosen for use in the esophagus and colon, and a 10 mm device was used for the stomach, duodenum and rectum. The overall success rate and complications were evaluated, with a particular emphasis on patients who had undergone ESD due to adenocarcinoma. In technical successful cases we included not only complete closing by using OTSCs, but also partial closing where complete closure with OTSCs is almost difficult. In overall clinical successful cases we included only complete closing by using only OTSCs perfectly. All the OTSCs were placed by 2 experienced endoscopists. The sites closed after ESD included not only the perforation site but also all defective ulcers sites.

RESULTS: A total of 23 patients [mean age 77 years (range 64-98 years)] underwent OTSC placement during the study period. The indications for OTSC placement were GI bleeding (n = 9), perforation (n = 10), fistula (n = 4) and the prevention of post-ESD duodenal artificial ulcer perforation (n = 1). One patient had a perforation caused by a glycerin enema, after which a fistula formed. Lesion closure using the OTSC alone was successful in 19 out of 23 patients, and overall success rate was 82.6%. A large lesion size (greater than 20 mm) and a delayed diagnosis (more than 1 wk) were the major contributing factors for the overall unsuccessful clinical cases. The location of the unsuccessful lesion was in the stomach. The median operation time in the successful cases was 18 min, and the average observation time was 67 d. During the observation period, none of the patients experienced any complications associated with OTSC placement. In addition, we successfully used the OTSC to close the perforation site after ESD in 6 patients. This was a single-center, retrospective study with a small sample size.

CONCLUSION: The OTSC is effective for treating GI bleeding, fistulae as well as perforations, and the OTSC technique proved effective treatment for perforation after ESD.

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Key words: Over-the-scope clip; Gastrointestinal bleed-
Table 1. The indications for OTSC placement were GI bleeding, perforations, fistulae and the prevention of post-ESD duodenal artificial ulcer perforation. ESD were performed because of dissection of adenocarcinoma. Maximum lesion size was defined as lesion diameter, not lesion surface area. The number of OTSCs to be used per patient was not decided until the lesion was completely closed. We used a twin grasper (Ovesco Endoscopy GmbH, Tuebingen, Germany) as a grasping device for all the patients. A 9-mm OTSC was chosen for use in the esophagus and colon, and a 10-mm device was used for the stomach, duodenum and rectum. Clinical success was defined by the results of a computed tomography scan and a blood analysis. Cases considered to be failures were those requiring hemostasis to control GI bleeding. In technical successful cases we included not only complete closing by using OTSCs, but also partial closing where complete closure with OTSCs is almost difficult. In overall clinical successful cases we included only complete closing by using only OTSCs perfectly.

All the OTSCs were placed by 2 experienced endoscopists. The sites closed after ESD included not only the perforation site but also all defect ulcers.

We obtained written, informed consent related to the use of OTSCs from all the patients.

Institution participating in the study
Kagawa University Hospital, Kagawa, Japan, participated in the study.

RESULTS
A total of 23 patients [mean age 77 years (range 64-98 years)] underwent OTSC placement during the study period. Of the 23 patients, 14 were male (60%) and 9 were female (40%). The indications for OTSC placement were GI bleeding (n = 9), perforation (n = 10), fistula (n = 4) and the prevention of post-ESD duodenal artificial ulcer perforation (n = 1). One patient had a perforation caused by a glycerin enema, after which a fistula formed. The perforations that were observed included iatrogenic perforations (n = 8) and hemorrhagic peptic ulcers (n = 2). The iatrogenic perforations included post-ESD artificial ulcer perforations (n = 6), a perforation by a local steroid injection into an ulcer following ESD to prevent gastric stenosis (n = 1), an esophageal perforation by a nasogastric tube (n = 1) (Figure 1) and a rectal perforation by a glycerin enema (n = 1). The fistulae included rectal fistulae (n = 2), a stomach-to-skin fistulae following percutaneous endoscopic gastrostomy (PEG) tube removal (n = 1) (Figure 2) and a stomach-to-brachial tube fistula (n = 1) (Figure 3).

The mean maximum size of the lesions was 23.1 mm (range 5 to 50 mm). The lesions were located in the esophagus (n = 1), the stomach (n = 10), the duodenum (n = 5), the sigmoid colon (n = 3) and the rectum (n = 4). The time required for the procedure was measured from the time that the OTSC was applied to the time that it was released in the lesion. The median operation time for the successful cases was 18 min (range 5 to 51 min). The
| No. | Sex | Age | Location                  | Primary disease                                      | Maximum lesion size (mm) | Prior treatment history | No. of OTSCs | Operation time (min) | Time from diagnosis (wk) | Technical/overall clinical successful | Additional treatment | Complication | Stay in hospital after OTSC placement (d) | Duration of follow-up (d) |
|-----|-----|-----|---------------------------|-----------------------------------------------------|--------------------------|------------------------|--------------|---------------------|--------------------------|----------------------------------------|-----------------------|--------------|------------------------------------------|------------------------|
| 1   | M   | 86  | Lower esophagus           | Iatrogenic perforation caused by stomach tube        | 20                      | None                   | 1            | 5                   | < 1                      | Yes/yes                               | None                  | None         | 6                                        | 56                     |
| 2   | M   | 74  | Stomach                   | Delayed perforation after ESD                       | 40                      | None                   | 2            | 24                  | < 1                      | Yes/yes                               | None                  | None         | 10                                       | 90                     |
| 3   | F   | 82  | Stomach                   | Perforation after ESD                               | 25                      | None                   | 2            | 20                  | < 1                      | Yes/yes                               | None                  | None         | 7                                        | 8                      |
| 4   | M   | 80  | Stomach                   | Peptic ulcer with bleeding                           | 15                      | HEMOSTATIC forces       | 1            | 8                   | < 1                      | Yes/yes                               | None                  | None         | 21                                       | 30                     |
| 5   | F   | 71  | Stomach                   | Peptic ulcer with perforation                        | 40                      | None                   | 2            | 23                  | < 1                      | Yes/yes                               | None                  | None         | 7                                        | 58                     |
| 6   | F   | 88  | Stomach                   | Gastrocutaneous fistula                              | 10                      | None                   | 1            | 18                  | > 4                      | Yes/yes                               | None                  | None         | 8                                        | 84                     |
| 7   | M   | 98  | Stomach                   | Bleeding due to Mallory-Weiss syndrome               | 12                      | None                   | 1            | 12                  | < 1                      | Yes/yes                               | None                  | None         | 6                                        | 15                     |
| 8   | M   | 73  | Duodenum                  | Para-anastomotic ulcer bleeding                      | 15                      | Clips                  | 2            | 21                  | < 1                      | Yes/yes                               | None                  | None         | 8                                        | 18                     |
| 9   | M   | 80  | Duodenal bulb             | Peptic ulcer with bleeding                           | 23                      | Clips and HEMOSTATIC forces | 2         | 30                  | < 1                      | Yes/yes                               | None                  | None         | 10                                       | 52                     |
| 10  | M   | 74  | Duodenal bulb             | Peptic ulcer with perforation                        | 5                       | None                   | 1            | 8                   | < 1                      | Yes/yes                               | None                  | None         | 13                                       | 194                    |
| 11  | F   | 73  | Duodenal bulb             | Prevention of post-ESD perforation                   | 25                      | None                   | 1            | 10                  | < 1                      | Yes/yes                               | None                  | None         | 7                                        | 95                     |
| 12  | M   | 75  | 3rd portion of duodenum   | Delayed perforation after ESD                       | 28                      | None                   | 2            | 36                  | < 1                      | Yes/yes                               | None                  | None         | 15                                       | 210                    |
| 13  | F   | 85  | Rectum                    | Rectovaginal fistula                                 | 15                      | None                   | 2            | 30                  | < 1                      | Yes/yes                               | None                  | None         | 9                                        | 28                     |
| 14  | F   | 88  | Rectum                    | Iatrogenic rectal perforation/fistula                | 25                      | None                   | 1            | 8                   | < 1                      | Yes/yes                               | None                  | None         | 10                                       | 30                     |
| 15  | M   | 73  | Stomach                   | Peptic ulcer with bleeding                           | 20                      | Clips and HEMOSTATIC forces | N/A        | N/A                 | 1-4                      | No/no                                 | Hemostatic forces       | N/A          | N/A                                       | N/A                    |
| 16  | M   | 64  | Stomach                   | Peptic ulcer with bleeding                           | 50                      | HEMOSTATIC forces       | N/A          | N/A                 | 1-4                      | No/no                                 | Hemostatic forces       | N/A          | N/A                                       | N/A                    |
| 17  | F   | 65  | Sigmoid colon             | Perforation after ESD                               | 35                      | None                   | 1            | 7                   | < 1                      | Yes/yes                               | None                  | None         | 8                                        | 160                    |
| 18  | F   | 83  | Sigmoid colon             | Perforation after ESD                               | 40                      | None                   | 3            | 16                  | < 1                      | Yes/yes                               | None                  | None         | 8                                        | 90                     |
| 19  | F   | 88  | Stomach                   | Perforation caused by a local injection needle       | 50                      | None                   | 3            | 51                  | 1-4                      | Yes/no                                 | Surgery               | N/A          | N/A                                       | N/A                    |
| 20  | M   | 65  | Rectum                    | Postoperative anastomotic ulcer bleeding            | 5                       | HEMOSTATIC forces       | 1            | 6                   | < 1                      | Yes/yes                               | None                  | None         | 8                                        | 14                     |
| 21  | M   | 65  | Rectum                    | Postoperative anastomotic ulcer bleeding            | 5                       | HEMOSTATIC forces       | 2            | 19                  | < 1                      | Yes/yes                               | None                  | None         | 7                                        | 30                     |
| 22  | M   | 73  | Sigmoid colon             | Refractory diverticular bleeding                     | 5                       | Clips                  | 1            | 7                   | < 1                      | Yes/yes                               | None                  | None         | 5                                        | 10                     |
| 23  | M   | 73  | Stomach                   | Gastrobronchial fistula                              | 28                      | Bronchial embolization  | 1            | 40                  | > 4                      | Yes/no                                 | May be given in future  | N/A          | N/A                                       | N/A                    |

OTSC: Over-the-scope clip; ESD: Endoscopic submucosal dissection; M: Male; F: Female; N/A: Not available; HSE: Hypertonic saline-epinephrine injection therapy.
There was no adjunct therapy used for OTSC placement in the 19 overall clinical success cases. In the two technical failure cases, we used coagulation forceps for additional hemostasis. All the patients were hospitalized for observation after the OTSC placement. The median hospital stay was 9 d (range 6-21 d).

**Complications**
During the observation period, none of the patients experienced any complications associated with OTSC placement.

**DISCUSSION**
The development of new NOTES devices has introduced advanced therapeutic techniques that can be used in minimally invasive treatments, including various full-thickness suturing devices that are applied in clinical practice. One of these devices is the OTSC system, the clinical utility of which has been reported in Europe and the United States. The OTSC system shows great potential for use in endoscopic treatments that require speed and simplicity. This system received a pharmaceutical license in Japan in November 2011. Although animal experiments and clinical studies have been performed in Europe and the United States, few clinical cases have been reported in Japan. We used the OTSC in NOTES animal experiments prior to its approval for clinical use.
humans. Recognizing its potential for use in Japan, we began using the OTSC clinically immediately after the pharmaceutical license was granted. We have employed this device in 23 patients within a short period in our hospital, with an overall success rate of 82%. Animal and clinical studies of the OTSC have demonstrated that gastrotic, duodenal or colonic perforations up to 15 mm in diameter can be completely closed with a single OTSC. For perforations up to 20 mm in diameter, closure can also be achieved using some OTSCs, which indicates that there is sufficient working space for the unobstructed use of the endoscope during NOTES[17]. There are reports that full-thickness closures of defects 18-27 mm in diameter can be performed using OTSC; however, it is difficult to completely close defects > 30 mm in diameter[18].

In the present series, OTSC closure was successful for wounds with a maximum diameter of ≤ 30 mm but unsuccessful in 1 case of refractory GI bleeding and 1 case of gastrobronchial fistula (Figure 3). Even in cases with a maximum wound diameter of > 30 mm, we placed the OTSC successfully because the tissue was well extensible and not hardened. In our clinical experience, unsuccessful OTSC closure had a chronic course and OTSC failures were due to chronic fibrotic changes and scarring at the perforation site. Specifically, we used OTSCs in 4 chronic patients and failed to close the perforation site in 3 of them (75%). It appears that wound closure with the OTSC is suitable for wounds with easy extensibility of the surrounding tissues; such lesions have little fibrosis and can be easily grasped by the twin grasper. Considering that successful closure was also achieved in cases with a rectal fistula < 20 mm in diameter or a gastrotubanous fistula after PEG removal (Figure 2), we believe that OTSC use should be considered when surgery is the only remaining option, provided that the lesion (even if presumably hardened) is ≤ 30 mm in diameter and can be sucked into the cap to lift the mucosa. In addition, the success of the OTSC closures in 4 cases with lesions > 30 mm suggests that this device can be used in acute cases with good extensibility of surrounding mucosa.

ESD was developed for en bloc removal of large gastric cancer, which decrease the risk of local recurrence, and specimens can be accurately evaluated by histological examination[19]. However, the procedure is associated with a high incident of complication with bleeding and perforation[20-22]. Now, bleeding has been good controlled with new hemostatic forceps and clips[23]. We also used the OTSC for the complete wound closure of post-ESD perforations in the stomachs of 2 patients who had undergone ESD for early gastric cancer. In both cases,

| Table 2 Relationship between each characters and overall clinical success rate n (%) |
|-----------------|-----------------|------------------|-------------------|
| Location | Overall clinical success |
|-----------------|-----------------|------------------|-------------------|
| Esophagus | 1 (100) |
| Stomach | 6 (60) |
| Duodenum | 100 |
| Colon | 3 (100) |
| Rectum | 4 (100) |
| Primary disease |
| GI bleeding | 9 (77) |
| Chronic fistulae | 4 (75) |
| Perforation | 11 (90) |
| Maximum lesion size (mm) |
| < 20 | 9 (100) |
| 20-30 | 6 (75) |
| > 30 | 4 (66) |
| Time from diagnosis (wk) |
| < 1 | 18 (100) |
| 1-4 | 0 (0) |
| > 4 | 1 (50) |

Figure 3 A gastric tube bronchial fistula following a subtotal esophagectomy for esophageal cancer. A: A gastric tube bronchial fistula occurred after a subtotal esophagectomy for esophageal cancer. Bronchial embolization was performed, but it failed to close the fistula; B: The authors attempted to close the fistula using over-the-scope clip (OTSC) but were unsuccessful. Although 1 OTSC was placed, mucosal hardening (resulting from the prolonged duration of the untreated ulcer) prevented the placement of the additional OTSCs required for closure; C: A chest-abdominal computed tomography scan revealed a gastrotubronchial fistula (arrow).
the lesions were located in the greater curvature of the stomach (Figure 4). Because it is anatomically thinner than other parts of the stomach, the greater curvature of the stomach is considered to be easy to perforate.\[24-29\]. In addition, because the knife is applied vertically to the mucosa during ESD, it is difficult to perform the procedure while maintaining an appropriate dissection depth into the submucosal layer. The endoscope must also be retroflexed\[24\]. These limitations have led to several cases in which our attempts to create a partial closure of an ulcer base using conventional clips caused the further extensive separation of the muscle layer and the subsequent need for surgery. In such cases, complete closure using the OTSC is thus preferred for a post-ESD ulcer in the greater curvature of the stomach, even if perforation is suspected.

The use of duodenal ESD is controversial among Japanese endoscopists because the narrow lumen of the duodenum makes it difficult to perform the procedure, and the base of a post-ESD duodenal ulcer is continuously exposed to bile, causing an increased incidence of delayed perforation compared with other ESD sites.\[30-35\]. Nevertheless, duodenal surgery is highly invasive because of the anatomical position. ESD should be preferentially performed instead of surgery if clinically indicated. The Japan Gastroenterological Endoscopy Society reported in April 2009 that the complete closure of a post-ESD duodenal ulcer using conventional clips helps prevent delayed perforation. However, conventional clips are too small and do not provide sufficient grip strength to achieve the complete closure of an ulcer base. Therefore, the OTSC, which is larger and provides greater grip strength, is recommended for the complete closure of post-ESD duodenal ulcers.\[36\].

At our hospital, patient 11 (Table 1) experienced a small perforation of a post-ESD ulcer that formed in the duodenal bulb, and the OTSC was used for its closure. In patient 12 (Table 1), the lesion occurred in the descending portion of the duodenum and was exposed to bile, indicating an increased risk of delayed perforation. Thus,
the ulcer was closed using the OTSC, which helped prevent perforation and bleeding.

We experienced 2 cases of OTSC closure for post-ESD ulcers in the colon. In both cases, the lesions were located in the sigmoid colon, with post-ESD perforations requiring complete wound closure. The wound was > 30 mm in diameter in both cases and was successfully closed using the OTSC.

We experienced 9 cases of GI bleeding that were treated with OTSCs. Widely used hemostatic procedures, such as hemostatic clips and local injections, are economically advantageous but sometimes fail to achieve complete primary hemostasis. The use of coagulation hemostasis with hemostatic forceps is also increasing because the reliable coagulation of exposed vessels under direct visualization can minimize the risk of rebleeding. However, the application of coagulation hemostasis to a deep ulcer or a thin wall of the duodenum is associated with a risk of perforation. For patients who do not tolerate surgery well and are in shock due to rebleeding or who do not respond to conventional treatment, the use of the OTSC should be considered. Based on these criteria, we applied OTSCs to the 9 patients with GI bleeding and achieved complete hemostasis in 7 of them. The remaining 2 patients with failed hemostasis using the OTSC system had a personal status ≥ 3 and could not tolerate open abdominal surgery. One of the patients had a large ulcer (50 mm in diameter) to which hemostasis with hemostatic forceps was applied. However, the patient experienced 2 episodes of shock due to bleeding from other sites of neovascularization. During the third episode of bleeding, ulcer closure with the OTSC was attempted but was unsuccessful due to a hardened ulcer base. Hemostasis with hemostatic forceps was again performed, after which no rebleeding was observed.

Hemostatic treatment of an anastomotic ulcer using the OTSC for was successful in 1 patient with a duodenal lesion and for 2 patients with lesions in the sigmoid colon (Figure 5). The aggressive treatment of bleeding with hemostatic forceps may cause perforations because anastomotic sites are usually thin and fragile. We consider the OTSC to be an effective tool for the treatment of lesions at anastomotic sites.

Regarding safety and complications, none of our patients treated with the OTSC reported any complications. Assessments performed 7 d after closure using the OTSC also revealed no displacements of the OTSC or tissue necrosis at the wound sites. Endoscopic examinations revealed OTSC losses in 2 cases: occurred 1 mo after OTSC placement for duodenal lesions, and the other occurred 2 mo after OTSC placement for colonic lesions. No associated complications were observed in either case. Other possible complications include mucosal damage caused by the teeth of the OTSC protruding out of the hood top during insertion. Therefore, special care should be taken when the OTSC is inserted into physiologically narrow sites, such as the esophageal entrance, pyloric ring or anal ring. There have been no reports of OTSCs causing mucosal deformation or stenosis of the gastrointestinal tract. However, we must consider the possibility that a failure to extract the fibrotic mucosa may result in the tissue being crushed by the twin grasper during the extraction of hardened tissue.

Based on our 23 cases and those reported in the literature, we consider OTSC to be a highly useful device that can be safely utilized in the treatment of GI perforations, fistulae and refractory bleeding. However, OTSC is not suitable for the closure of chronic lesions with hard, severely fibrotic wounds because it is difficult to draw such a lesion into the top of the device. However, we have used the OTSC to close post-ESD perforations with a 100% success rate. Although our sample size was small, we believe that the OTSC is a viable treatment option for post-ESD perforation.

**COMMENTS**

**Background**

Recently, over-the-scope clip (OTSC) devices have been used for gastrointestinal (GI) bleeding, fistulae and perforations in the United States and several European countries. OTSC devices became pharmaceutically licensed in Japan in August 2011. The authors have reported their experiences with the OTSC and the outcomes of several cases in Japan. The aims of the present study were to retrospectively review the results of OTSC use in the authors’ hospital and to examine the feasibility of using the OTSC to completely close perforations after endoscopic submucosal dissection (ESD) for early GI cancers.

**Research frontiers**

Historically, the standard treatment for GI perforations has been surgery. Recently, invasive endoscopic treatments, such as ESD and natural orifice transluminal endoscopic surgery (NOTES), have provided alternative approaches to surgery. However, the devices used to treat complications following endoscopic treatments are less convenient and not as safe. OTSCs have been used to treat GI bleeding, fistulae and perforations in several countries. In this study, the authors retrospectively report the results of using the OTSC in their hospital. They also discuss the potential use of the OTSC to completely close perforations after ESD for early GI cancers.

**Innovations and breakthroughs**

This is the first retrospective study of the OTSC in Japan, and it includes more cases of post-ESD perforation closure compared with other published reports on OTSC. All the post-ESD perforation closure cases in the present study were successes. Thus, the authors consider OTSC to be a possible tool for the treatment of perforations after ESD.

**Applications**

Based on the present 23 cases and those reported in the literature, the authors assert that the OTSC is useful and safe for the treatment of GI perforations, fistulae and refractory bleeding.

**Terminology**

ESD is the only nonsurgical, endoscopic method of treating early GI cancers; NOTES, a fusion of flexible endoscopy and operative techniques, is a less invasive form of treatment than surgery.

**Peer review**

The OTSC is an interesting and novel device that enhances the armamentarium of therapeutic gastroenterologists. This report illustrates the use of this novel device, which facilitates interventions that were previously impossible to perform endoscopically.

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