Criteria for the use of conventional clip and over-the-scope clip for closure of mucosal defects after duodenal endoscopic submucosal dissection

Ryuhei Jinushi (✉ gk3273@icloud.com )
Saitama Medical University International Medical Center

Tomoaki Tashima
Saitama Medical University International Medical Center

Ryo Sato
Saitama Medical University International Medical Center

Kengo Komori
Saitama Medical University International Medical Center

Takahiro Shin
Saitama Medical University International Medical Center

Rie Terada
Saitama Medical University International Medical Center

Rie Shiomi
Saitama Medical University International Medical Center

Takahiro Muramatsu
Saitama Medical University International Medical Center

Tsubasa Ishikawa
Saitama Medical University International Medical Center

Akashi Fujita
Saitama Medical University International Medical Center

Yuki Tanisaka
Saitama Medical University International Medical Center

Yumi Mashimo
Saitama Medical University International Medical Center

Masafumi Mizuide
Saitama Medical University International Medical Center

Tomonori Kawasaki
Saitama Medical University International Medical Center

Shomei Ryozawa
Saitama Medical University International Medical Center
Abstract

Purpose

Over-the-scope clip (OTSC) is used for treatment of gastrointestinal perforation, postoperative anastomotic leakage, and for mucosal defect closure after duodenal endoscopic submucosal dissection (ESD). However, OTSCs are expensive and associated with fatal complications; therefore, proper OTSC usage is necessary. There are no clear criteria for OTSC use for mucosal defect closure after duodenal ESD. Therefore, we examined the closure outcomes achieved using OTSCs or conventional clips for patients that underwent duodenal ESD. We also analyzed the resected specimen area and preoperative estimated size of tumors treated with each method to determine the criteria for using either OTSC or conventional clip.

Methods

Endoscopic resection was performed for 133 superficial duodenal epithelial tumors at our institution from April 2017 to February 2022. Complete closure of mucosal defects after duodenal ESD was attempted for 82 tumors; these were divided into the OTSC group and the control group (for which conventional clips were used). Closure outcomes were analyzed.

Results

The overall rate of complete mucosal defect closure in the OTSC and control groups was 98.8% (95% confidence interval = 93.39–99.97%). There were significant differences in the median estimated tumor size (20 mm vs 15 mm; p < 0.001) and median resected specimen area (339.1 mm$^2$ vs 169.6 mm$^2$; p < 0.001) between the groups.

Conclusion

If the estimated preoperative tumor size is \( \leq 18 \) mm, complete closure of mucosal defects after duodenal ESD can be achieved with only conventional clips. Based on this study, we suggest that OTSC is not necessary for small lesions.

Introduction

Over-the-scope clip (OTSC; Ovesco Endoscopy GmbH, Tübingen, Germany) is useful for treating gastrointestinal perforation, postoperative anastomotic leakage, and bleeding [1]. In addition, OTSCs are useful for complete closure of mucosal defects to prevent adverse events due to exposure to bile or pancreatic juice after duodenal endoscopic submucosal dissection (ESD) [2–4]. Additionally, there have
been reports of endoscopic resection of duodenal tumors using OTSCs [5], and OTSCs are gaining recognition in many fields. In cases of gastrointestinal perforations, closure with OTSCs or through-the-scope clips (TTSCs) should be considered if the perforation size is < 2 cm; however, a combination of TTSCs and PolyLoop ligating device or endoscopic sutures should be considered if the size is ≥ 2 cm [6]. However, no studies have clearly demonstrated the size of mucosal defect that requires OTSCs or the criteria for using OTSCs to close mucosal defects after duodenal ESD. The rates of delayed bleeding and delayed perforation after duodenal ESD are very high compared to those observed after ESD of other organs, which is largely because of the exposure of duodenal mucosal defects to bile and pancreatic juice [7, 8]. Therefore, complete closure of mucosal defects is necessary for preventing severe adverse events, and OTSCs are often used for this purpose [2–4]. Although OTSC usage results in a high rate of complete closure (> 90%), there are some caveats. The OTSC is difficult to deploy if the tumor is in a flexure, such as the superior or inferior duodenal angle, and there is a slight risk of critical bleeding or perforation if the OTSC is deployed incorrectly [2]. Furthermore, OTSCs are expensive (approximately $800). Therefore, from the standpoint of medical costs, it is desirable to avoid their overuse and utilize them appropriately. This study aimed to assess appropriate use of OTSCs based on the area of the resected specimen after duodenal ESD and to estimate the preoperative tumor size that should be an indication for OTSC rather than conventional clip use. Our study can be defined by the following clinical question: what is the area of the resected specimen that would normally allow the closure of a mucosal defect with conventional clips only?

**Material And Methods**

**Study design and ethical statements**

This retrospective cohort study was conducted at Saitama Medical University International Medical Center in Japan. It was approved by the Institutional Review Board of the medical center (institutional ID: 20–249) and performed in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

**Patients**

Endoscopic resection was performed for 133 superficial duodenal epithelial tumors at our institution from April 2017 to February 2022. Among them, 7 ampullary tumors, 2 tumors observed during laparoscopy and endoscopy cooperative surgery, and 33 tumors observed during endoscopic mucosal resection were excluded. We also excluded 9 tumors in the duodenal bulb. Finally, 82 tumors for which complete mucosal defect closure after duodenal ESD was attempted were included in the analysis. The cases were divided into two groups: the OTSC group consisted of 55 cases and the control group (for which conventional clips only were used) consisted of 27 cases (Fig. 1).

**Preparation For Duodenal Esd**
In general, duodenal endoscopic mucosal resection was performed under intravenous anesthesia in the endoscopy room, and duodenal ESD was performed under general anesthesia in the operating room. However, the procedure was performed under intravenous anesthesia when the risk of performing duodenal ESD under general anesthesia was estimated to be high based on the patient’s general condition. Under intravenous anesthesia, our endoscopists adjusted the dosage of midazolam, pethidine, and dexmedetomidine according to the patient’s condition. The antispasmodic drugs used were scopolamine for patients who had no cardiac disease or benign prostatic hyperplasia, and glucagon for patients who had these conditions. All duodenal ESDs were performed by a single endoscopist (T.T.) who had experience performing more than 1,500 ESD procedures, including at least 300 each in the esophagus, stomach, and colon. All ESD procedures were performed using a therapeutic endoscope (GIF-H290T or GIF-Q260J; Olympus, Medical Systems Co., Tokyo, Japan) with a transparent cap (D-201-11804; Olympus). Regarding endoscopic devices, we used a 1.5-mm DualKnife J (KD655Q; Olympus) to perform mucosal incision or submucosal dissection. Depending on the circumstances of each case, a 3.5-mm Clutch Cutter (Fujifilm Co, Tokyo, Japan) was used as an adjunct. The endoCUT I (effect 1, duration 4, interval 1), forced coagulation (effect 2, 45 W), and soft coagulation (effect 4, 60 W) modes of an electrosurgical generator (VIO 300D; ERBE Elektromedizin, Tübingen, Germany) were used for mucosal incision, submucosal dissection, and hemostatic procedure, respectively. A local injection of 0.4% sodium hyaluronate (MucoUp®; Boston Scientific, Tokyo, Japan) combined with a small amount of indigo carmine was administered into the submucosa to firmly elevate it and ensure optimal visualization.

**Details Of Both Groups And Definitions Of Outcomes**

This study included 82 cases for which complete closure of mucosal defects after duodenal ESD was attempted. Of these, 55 cases were in the OTSC group and 27 were in the control group. Complete closure of mucosal defects was successfully achieved for 81 cases; however, it was unsuccessful for one case in the OTSC group.

**OTSC group**

At least one OTSC was used in each case. Depending on the size of the mucosal defect, conventional clips (EZ Clip, HX-610-135, HX-610-090L; Olympus) and PolyLoop ligating device sutures (HX21L1, MAJ339; Olympus) were used with OTSCs (Fig. 2).

**Control group**

Only conventional clips were used (Fig. 3).

**Definitions**

En bloc resection: a one-piece resection that included the entire tumor
Procedure time: the time from the initial mucosal incision to tumor resection

Resected specimen area: This was calculated using the following equation: the largest diameter of the resected specimen (mm)/2 × the smallest diameter of the specimen (mm)/2 × 3.14.

Intraoperative perforation: perforation that occurred during duodenal ESD

Delayed perforation: perforation diagnosed using computed tomography after duodenal ESD

Delayed bleeding: hemorrhage that required additional endoscopic hemostasis after duodenal ESD

Resectability: This was classified into three categories based on the final pathological diagnosis, as follows: R0, both the horizontal and vertical margins were negative; RX, either the horizontal or the vertical margin was unclear; and R1, either the horizontal or the vertical margin was positive.

Surgery due to adverse events: cases that required surgery because of duodenal ESD-related complications

Closing time: the time from re-insertion of the endoscope after specimen retrieval until the end of the closure procedure

Additional treatment: a case that required endoscopic treatment or surgery due to adverse events associated with OTSC application

**Statistical analysis**

The primary objective of this study was to estimate the area of possible complete closure of mucosal defects after duodenal ESD in the OTSC and control groups. First, we compared patient characteristics and duodenal ESD outcomes of the two groups in order to identify case bias, if any. Thereafter, we focused on the preoperatively estimated tumor size and resected specimen area, and calculated their median values for each closure method. Binary variables of the two groups were compared using Pearson’s chi-square test, and continuous variables were compared using Mann–Whitney U test or Student’s t-test. All analyses in this study were performed using STATA® version 17 (StataCorp, College Station, TX, USA). P < 0.05 was considered statistically significant.

**Results**

**Characteristics of the patients**

The following background characteristics of the patients were compared between the OTSC (n = 55) and control (n = 27) groups: age, sex, tumor location, occupied circumference, macroscopic classification, estimated tumor size, preoperative biopsy findings, and antithrombotic therapy. Between the two groups, there were significant differences in sex (47.8% female vs. 11.1% male; p = 0.001), median estimated
tumor size (20 mm vs. 15 mm; p < 0.001), and antithrombotic therapy use (0% vs. 11.1%; p = 0.012) (Table 1).

Outcomes Of Duodenal Esd

The outcome measures used to evaluate the two groups were en bloc resection, procedure time, resected tumor diameter, largest diameter of the resected specimen, smallest diameter of the resected specimen, resected specimen area, intraoperative perforation, delayed bleeding, delayed perforation, surgery due to adverse events, final pathological diagnosis, lymphovascular invasion, resectability, and recurrence. Between the groups, there were significant differences in the median resected tumor diameter (20 mm vs. 15 mm; p < 0.001), median largest diameter of the resected specimen (24 mm vs. 18 mm; p < 0.001), median smallest diameter of the resected specimen (18 mm vs. 12 mm; p = 0.0001), and median resected specimen area (339.1 mm$^2$ vs. 169.6 mm$^2$; p < 0.001) (Table 2).

Outcomes Of Complete Mucosal Defect Closure After Duodenal Esd

The combined rate of complete mucosal defect closure in the two groups was 98.8% (95% confidence interval = 93.39–99.97%). There was no significant difference in the rate of complete mucosal defect closure and closing time between the two groups (Table 3). The average number of OTSCs used in the OTSC group (n = 55) was 1.4 (standard deviation = 0.56), and the OTSC was deployed using the suction method in 90.9% (n = 50) and the twin-grasper method in 9.1% (n = 5) of cases. There was one case in which the OTSC was deployed to the ulcer during ESD and complete closure failed; however, none of the patients required additional treatment because of adverse events associated with OTSC (Table 4).

Discussion

The risks of delayed bleeding and delayed perforation caused by exposure to bile and pancreatic juice are very high, especially during duodenal ESD. In this study, we aimed to determine the indication for the use of OTSCs rather than conventional clips after duodenal ESD, based on the preoperative tumor size and area of the resected specimen. The effectiveness of prophylactic closure of mucosal defects after duodenal ESD has been reported [9], and OTSCs are often used for this method [2–4]. The use of OTSCs allows for complete and firm closure of mucosal defects after duodenal ESD. In this study, the rate of complete closure of mucosal defects with OTSCs was very high (> 95%); however, there are some caveats. The OTSC may be difficult to deploy if the tumor is located in a flexure, such as the superior or inferior duodenal angle, and there is a small risk of serious bleeding or perforation if the OTSC is incorrectly deployed. OTSC removal devices have been developed in other countries for correction of failed OTSC deployment [10]; however, such correction is not practical. OTSC deployment is characterized by a single attempt and requires skill. It has been reported that multiple OTSC deployments have resulted in a gap between OTSCs and perforation in the same area because of exposure to bile or pancreatic juice [11]. Furthermore, OTSCs cost approximately $800 per unit; an additional $900 is required if the twin-
grasper method is used. Therefore, considering the medical costs, it is desirable to avoid the overuse of OTSCs and use them appropriately.

We compared the closure of mucosal defects after duodenal ESD between the OTSC and control groups and examined the appropriate criteria for the use of OTSCs based on the resected specimen area. The median resected specimen areas of the OTSC and control groups were 339.1 mm$^2$ (interquartile range [IQR] = 235.5–604.5 mm$^2$) and 169.6 mm$^2$ (IQR = 141.3–266.9 mm$^2$), respectively. Additionally, the median estimated preoperative tumor sizes were 20 mm (IQR = 18–30 mm) and 15 mm (IQR = 12–15 mm) in the OTSC and control groups, respectively. Spearman's rank correlation coefficient between the estimated preoperative tumor size and resected specimen area was 0.847 (p < 0.001), indicating a strong correlation. Unless the tumor shape is very distorted, the resected specimen area can be calculated using the estimated preoperative tumor size. In the control group of the present study, the median estimated preoperative tumor size was 15 mm (minimum = 10 mm; IQR = 12–15 mm; maximum = 18 mm), and the median resected specimen area estimated from the estimated preoperative tumor size was 176.6 mm$^2$ (minimum = 78.5 mm$^2$; IQR = 113.0–176.6 mm$^2$; maximum = 254.3 mm$^2$). Based on the fact that the maximum estimated resected specimen area (254.3 mm$^2$) ranged from 25–75% of the control group measurements, and that complete closure of the mucosal defect was possible for all cases in the control group during this study, closure of the mucosal defect was possible using only conventional clips if the estimated preoperative tumor size was ≤ 18 mm. Therefore, for the closure of mucosal defects after duodenal ESD, complete closure can be expected with conventional clips only if the estimated preoperative tumor size is ≤ 18 mm. If the size is > 18 mm, it may be advisable to use a combination of OTSCs, PolyLoop ligating device sutures, clip-and-threads [12], or conventional clips for complete closure of the mucosal defect. During duodenal ESD, for which the risk of adverse events is much higher than that for ESD in other organs, it is useful to estimate the resected specimen area based on the estimated preoperative tumor size and to consider the strategy for closing mucosal defects after the procedure. This will enable safe and economical duodenal ESD in the future. Recently, a re-openable clip (SureClip 16 mm; Micro-tech, Nanjing, China), which has a larger opening width than a conventional clip, has become popular (Fig. 4). In the future, we would like to study the outcomes of mucosal defect closure with re-openable clips and OTSCs among a larger number of patients, and establish clear criteria for their use in order to achieve more economical medical care.

In addition to the limitation of this study as a single-center retrospective study, the performance of the procedure by a single endoscopist could have led to crucial selection bias. However, duodenal ESD is not as common as ESD in other organs and should be performed by a skilled endoscopist at that facility, so this study design is acceptable. We would like to accumulate more cases in the future in order to verify whether our results are common in clinical practice.

**Conclusion**
If the estimated preoperative tumor size is \( \leq 18 \text{ mm} \), complete closure of mucosal defects after duodenal ESD can be achieved with only conventional clips. Based on the results of this study, we suggest that OTSC is not necessary for small lesions. It would contribute to more appropriate use of OTSC in the future.

**Abbreviations**

OTSC, Over-the-scope clip

EMR, endoscopic mucosal resection

ESD, endoscopic submucosal dissection

EFTR, endoscopic full-thickness resection

LECS, laparoscopy and endoscopy cooperative surgery

SDETs, superficial duodenal epithelial tumors

SNADETs, superficial non-ampullary duodenal epithelial tumors

TTSCs, through-the-scope clips

CI, confidence interval

SD, standard deviation

IQR, interquartile range

Min, minimum

Max, maximum

**Declarations**

**Competing interests**

The authors declare no competing interests.

**AUTHORS’ CONTRIBUTIONS**

Study conception and design: RJ, TT

Acquisition of data: RJ, TT

Analysis and interpretation of data: RJ
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References


Tables

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Figures
133 patients with 133 SDETs were treated by endoscopic resection in Saitama Medical University International Medical Center between April 2017 and February 2022.

- 7 patients with 7 ampullary tumors were excluded.
- 2 patients with 2 SNADET treated by LECS was excluded.
- 33 patients with 33 SNADET treated by EMR were excluded.

91 patients with 91 SNADET were treated by ESD in Saitama Medical University International Medical Center between April 2017 and February 2022.

- 9 patients in the duodenal bulb were excluded.

82 patients with 82 SNADET were treated by ESD in Saitama Medical University International Medical Center between April 2017 and February 2022.

Attempts at complete mucosal defect closure

- OTSC-group is 55 patients.
- Control-group is 27 patients.

**Figure 1**

**Study flowchart**

SDETs, superficial duodenal epithelial tumors; SNADET, superficial non-ampullary duodenal epithelial tumors; LECS, laparoscopy and endoscopy cooperative surgery; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; OTSC, over-the-scope clip
Figure 2

Combination of conventional clips, PolyLoop ligating device sutures, and over-the-scope clips for closing a huge mucosal defect

(a) Mucosal defect in the descending part of the duodenum after endoscopic submucosal dissection (ESD). The resected specimen diameter was 61×60 mm. The resected tumor diameter was 60×55 mm.

(b) The mucosal defect was reduced using PolyLoop ligating device sutures and conventional clips.

(c) Subsequently, the defect was closed with two over-the-scope clips (OTSCs) using the aspiration method. The remaining mucosal defect was completely closed with additional conventional clips. The closure time was 45 minutes.

Figure 3

Use of only conventional clips to close mucosal defects

(a) Mucosal defect in the descending part of the duodenum after endoscopic submucosal dissection (ESD). The resected specimen diameter was 26×20 mm. The resected tumor diameter was 18×18 mm.

(b) First, the center of the mucosal defect was closed with a conventional clip.
(c) Next, more conventional clips were added to the remaining mucosal defect, and complete closure was performed. The closure time was 18 minutes.

**Figure 4**

**Use of a re-openable clip to close mucosal defects**

(a) Mucosal defect in the descending part of the duodenum after endoscopic submucosal dissection (ESD). The resected specimen diameter was 28×20 mm. The resected tumor diameter was 22×18 mm.

(b) First, the center of the oral side of the mucosal defect was grasped, and closure was attempted. Because the clip is a re-openable clip, it can be used as many times as necessary.
(c) Release of the clip.

(d) Next, conventional clips were added to the residual mucosal defect, and it was completely closed. The closure time was 15 minutes.