Accepted Manuscript

Submission Date: 2024-05-28
Accepted Date: 2024-12-07
Accepted Manuscript online: 2024-12-16

Endoscopy International Open

Endoscopic closure using a dedicated device following gastric endoscopic submucosal dissection: a multicenter, prospective, observational pilot study

Kazuo Shiotsuki, Kohei Takizawa, Yohei Nose, Yuki Kondo, Hitoshi Homma, Taisuke Inada, Mao Daikaku, Kosuke Maehara, Shin-ichiro Fukuda, Hironori Aoki, Yorinobu Sumida, Hirotada Akiho, Jiro Watari, Kiyokazu Nakajima.

Affiliations below.

DOI: 10.1055/a-2503-1684

Please cite this article as: Shiotsuki K, Takizawa K, Nose Y et al. Endoscopic closure using a dedicated device following gastric endoscopic submucosal dissection: a multicenter, prospective, observational pilot study. Endoscopy International Open 2024. doi: 10.1055/a-2503-1684

Conflict of Interest: The authors declare that they have no conflict of interest.

This study was supported by Japan Consortium for Advanced Surgical Endoscopy, J-CASE Research Grant

Trial registration: jRCT1072220065, Japan Medical Association Clinical Trial Registry (http://www.jmacct.med.or.jp/), Prospective

Abstract:
Background and study aims: The development of a simple, optimized closure method for mucosal defects left by gastric endoscopic submucosal dissection (ESD) is warranted. Herein, we developed a novel and dedicated closure device called FLEXLOOP and aimed to assess the feasibility and safety of the closure using FLEXLOOP following gastric ESD.
Patients and Methods: This multicenter, prospective, observational study enrolled patients clinically diagnosed with gastric neoplasms < 30 mm in size. Following gastric ESD, closure of the mucosal defect was performed using a FLEXLOOP with standard clips. The primary outcome was the complete closure rate. The secondary outcomes were procedure time, number of clips, sustained closure rate on second-look endoscopy on postoperative days (PODs) 5–7, and rate of post-ESD bleeding.
Results: Overall, 35 patients were included in this study. The median specimen size was 32 mm. The mucosal defect was completely closed in 31 (89%; 95% confidence interval, 73–99%) patients and incompletely closed in 4 (11%) patients. The median closure time was 11 min, and the median number of clips was 10. Second-look endoscopy performed on PODs 5–7 demonstrated sustained, partially sustained, and unsustained closures in 7 (20%), 22 (63%), 6 (17%) patients, respectively. Post-ESD bleeding and complications related to FLEXLOOP were not observed.
Conclusions: Closure using FLEXLOOP is feasible and safe. Our technique using this new device can be an attractive option for more easier approach to closing mucosal defects. However, further clinical research to confirm that this technique can prevent delayed complications is warranted.

Corresponding Author:
Dr. Kohei Takizawa, Koyukai Shin-Sapporo Hospital, Gastroenterology and Endoscopy, Sapporo, Japan, koh.takizawa@gmail.com

Affiliations:
Kazuo Shiotsuki, Kitakyushu Municipal Medical Center, Department of gastroenterology, Kitakyushu, Japan
Kazuo Shiotsuki, Kanagawa Cancer Center, Gastroenterology, Yokohama, Japan
Kohei Takizawa, Koyukai Shin-Sapporo Hospital, Gastroenterology and Endoscopy, Sapporo, Japan
[...]

Kiyokazu Nakajima, Osaka University Graduate School of Medicine, Department of Gastroenterological Surgery, Suita, Japan

Introduction

Endoscopic submucosal dissection (ESD) is an established specialized technique that enables the en bloc resection of neoplasia [1]. With the advancement of technology [2] and expanded indications for treatment [3,4], ESD for early gastric cancer (EGC) has spread worldwide, and its long-term outcomes are acceptable as a standard treatment instead of gastrectomy [5].

However, adverse events, such as post-ESD bleeding or delayed perforation, have yet to be eliminated. In post-ESD bleeding, the risk is 11.4–29 % in high to very high-risk cases and should not be ignored as an ESD-related complication [6], and it is a concern to overcome this problem [7].

Because the ulcer left by gastric ESD remains open, exposure to gastric acid or bile juice induces adverse events. Various techniques and special devices have been proposed to close or protect the mucosal defects following gastric ESD to reduce the risk of such consequences. However, these methods have not been widely disseminated mainly owing to technical difficulties and/or cost-effectiveness [8-10].

We also reported the efficacy of endoloop closure for mucosal defects following gastric ESD in high-risk patients [11], but the procedure was not straightforward.

Endoloop is a device for ligating gastrointestinal polyps, not designed for mucosal closure; therefore, we attempted to develop a dedicated device for the closure of mucosal

defects. Finally, we developed a novel, simple, and dedicated closure device called FLEXLOOP (Hakko Co., Ltd., Nagano, Japan), consisting of a nylon thread and an outer sheath (Fig. 1) [12]. The clinical feasibility of closure using FLEXLOOP with endoscopic clips has not yet been investigated; thus, this multicenter, prospective, observational pilot study aimed to investigate the feasibility and safety of using FLEXLOOP.

Materials and methods

Patients

This study was conducted at Kitakyushu Municipal Medical Center and Koyukai Shin-Sapporo Hospital between November 2022 and August 2023. The current study was approved by each institutional review board in accordance with the Declaration of Helsinki and registered in the Japan Registry of Clinical Trials. All patients provided written informed consent to participate in this study and underwent all the endoscopic procedures.

The inclusion criteria were as follows: (a) a single clinically diagnosed gastric adenoma or EGC < 30 mm in size, which matched the guidelines for ESD and endoscopic mucosal resection for EGC [13]; (b) age > 20 years; and (c) Eastern Cooperative Oncology Group performance status of 0–2.

If the patients received antithrombotic therapy, we performed ESD by following the guidelines for the management of patients receiving antithrombotic therapy [14].

Endoscopic submucosal dissection (ESD) and closure of mucosal defect using FLEXLOOP with endoclips

ESD was performed using an ITknife2 (KD-611L; Olympus, Tokyo, Japan) or ORISE ProKnife (M00519361; Boston Scientific Japan, Tokyo, Japan), GIF-290T (Olympus, Tokyo, Japan), a flexible overtube (MD-48518; SB-KWASUMI LABORATORIES, Tokyo, Japan), and a high-frequency generator (VIO3; ERBE, Tubingen, Germany). Radial Jaw Hot Biopsy Forceps (Boston Scientific Japan, Tokyo, Japan) or Hemostat-Y (H-S2518; PENTAX MEDICAL Japan, Tokyo, Japan) was used to perform hemostatic coagulation for intraoperative bleeding and visible vessels on the post-ESD ulcer bed [15]. Although the level of evidence is relatively low, post-ESD coagulation is considered a standard procedure in Japan because of its simplicity and potential to reduce the risk of delayed bleeding.

Closure of the mucosal defect using FLEXLOOP with clips (Sure Clip, 11mm; MC Medical, Tokyo, Japan) was performed after gastric ESD. The closure technique involved the following steps: (1) the outer sheath of FLEXLOOP was externally

attached on the side of the standard gastrointestinal endoscope; (2) the endoscope was advanced through the overtube, and the loop was deployed and anchored along with the mucosal defect with clips; (3) the defect was circumferentially narrowed with additional several clips, as the loop was tightened by pushing the outer sheath (Fig. 2 and Supplementary Video 1); and (4) after closure, the tail of the loop was cut using endoscopic scissor forceps (FS-410L; Olympus, Tokyo, Japan). All endoscopists were lectured on the closure procedure using FLEXLOOP by watching a video case series. Closure using FLEXLOOP with clips was performed by both experts and nonexperts, with experts defined as board-certified endoscopists.

Management after ESD

Omeprazole (20 mg/day) was intravenously administered to patients on the day of the ESD procedure and the following day. Laboratory data and physical examinations were performed on postoperative day (POD). A soft food diet and oral potassium-competitive acid blocker (P-CAB) (20 mg/day) or oral proton pump inhibitor (PPI) was started on POD 2 or 3. Second-look endoscopy was performed on PODs 5–7 to evaluate the closure status. If there were no complications, such as bleeding or perforation, the patients were discharged after POD 8. Oral P-CAB or PPIs were administered for a

minimum of 8 weeks, and a third-look endoscopy in the outpatient department was performed 4 or 5 weeks later to assess the ESD site.

Outcome measurement

The primary outcome was the success rate of complete closure using FLEXLOOP with endoclips. The completeness of closure was divided into three categories: the mucosal defect was completely closed (complete), partially closed (incomplete), and not closed (failure). Complete closure was defined as no ulcer bed visible on endoscopic findings after closure, incomplete closure was defined as slight visibility of the ulcer bed, and failure was defined as closure that could not be performed, and closure was assessed by two endoscopists. The secondary outcomes were procedure time, number of FLEXLOOP, number of clips used, success rate of complete closure related to location or circumference, rate of sustained closure on second-look endoscopy PODs 5–7, rate of sustained closure at second-look endoscopy PODs 5–7 related to location or circumference, post-ESD bleeding rate, state of closure site approximately 4 or 5 weeks after discharge, and adverse event-related closure using FLEXLOOP. The closure time was defined as the time from opening the loop in the stomach to cutting the loop using the scissor forceps. Sustained closure at the second-look endoscopy PODs 5–7 was defined as

sustained when the ulcer bed was not visible, partially sustained when the ulcer bed was partially visible, and unsustained when the ulcer bed was fully visible. Post-ESD bleeding was defined as symptoms, such as melena, hematemesis, or decreased hemoglobin level (≥ 2.0 g/dL), that required emergency endoscopy.

Sample size calculation

Previously, Choi et al. reported that complete closure rate using only clips was 62% following gastric ESD [16]. Our study group hypothesized that the complete closure rate using FLEXLOOP with clips would be increased 20% than closure using only clips. Based on the parameters $\alpha = 0.05$ (one-sided level) and power $(1-\beta) = 0.8$, a sample size calculation with a one arm binominal model required 31. Assuming dropout cases, the final target sample size was 35.

Results

Patients and ESD procedures

Thirty-five patients were enrolled between November 2022 and August 2023, all of whom underwent ESD and protocol management. There were 27 men and 8 women, with a median age of 72 (range, 47–87) years. Among them, seven patients received antithrombotic therapy, and all of them received a single antithrombotic therapy

(antiplatelet drug in five patients, anticoagulant drug in two patients). No heparin bridge replacement was performed.

En bloc resection was achieved in all patients, the median ESD procedure time was 33 (range, 12–107) min, and no intraoperative or delayed perforation occurred. The median resected specimen and pathological lesion sizes were 32 (range, 22–56) mm and 10 (range, 3–35) mm, respectively. The baseline characteristics and outcomes of ESD are shown in Tables 1 and 2, respectively.

Outcomes of closure using FLEXLOOP

The mucosal defect was completely closed in 31 (89%; 95% confidence interval, 73–99%) patients and incompletely closed in 4 (11%) patients, and failure case was not observed. The median procedure time for closure was 11 (range, 8–43) min, the median number of FLEXLOOP was 1 (range, 1–2), and the median number of clips used was 10 (range, 8–17).

The success of complete closure related to location was as follows: upper third, 3 of 4 (75%) patients; middle third, 14 of 16 (88%) patients; and lower third, 14 of 15 (93%) patients. The success of complete closure related to circumference was as follows: greater curvature, 10 of 12 (83%) patients; posterior wall, 10 of 11 (91%) patients; lesser curvature, 5 of 6 (83%) patients; and anterior wall, 6 of 6 (100%) patients.

Second-look endoscopy performed on PODs 5–7 demonstrated sustained closure in 7 (20%) patients, partially sustained closure in 22 (63%) patients, and unsustained closure in 6 (17%) patients.

Sustained closure on PODs 5–7 related to location was as follows: upper third, 1 of 4 (25%) patients; middle third, 3 of 16 (19%) patients; and lower third, 3 of 15 (20%) patients. Sustained closure on PODs 5–7 related to circumference showed the following: greater curvature, 3 of 12 (25%) patients; posterior wall, 2 of 11 (18%) patients; lesser curvature, 0 of 6 (0%) patients; and anterior wall, 2 of 6 (33%) patients.

The rate of post-ESD bleeding was 0%. The risk categories of post-ESD bleeding using the BEST-J score prediction model [6] showed that low risk was observed in 27 (77%) patients, intermediate risk in 5 (14%) patients, and high risk in 3 (9%) patients.

Two patients were at risk of lymph node metastasis after the pathological assessment of ESD specimens; therefore, they underwent additional surgery to prevent distant metastasis. Third-look endoscopy was performed in the remaining 33 patients approximately 4 or 5 weeks after discharge. The mucosal defect developed hearing stage scar formation in 21 (64%) patients, the mucosal defect was opened in 9 (27%) patients, and the mucosal closure remained in 3 (9%) patients. Of the 21 scar formation cases, 19 (90%) had complete closure, and 2 (10%) had incomplete closure; of the nine

opened cases, 8 (88%) had complete closure, and 1 (12%) had incomplete closure; All three of the three remained cases were complete closure.

Adverse events related to the procedure using FLEXLOOP with endoclips were not reported. The outcomes of closure using FLEXLOOP with endoclips are shown in Tables 3.

Closure was performed by experts in 19 (54%) patients and by nonexperts in 16 (46%) patients. We compared the outcome of closure between experts and nonexperts. The baseline and closure outcome between experts and nonexperts are summarized in Table 4. No significant differences were observed in location and circumference between experts and nonexperts. The complete closure rates were 84% (16/19) in experts and 94% (15/16) in nonexperts, with no statistically significant difference ($p = 0.60$). The closure time was longer for experts than for nonexperts ($p = 0.04$). Tumor size was larger in the expert group than in the nonexpert group, but there was no significant difference between the two groups ($p = 0.09$).

We investigated the risk factors for incomplete closure using FLEXLOOP with endoscopic clips. The details are summarized in Table 5. The closure time was longer in the incomplete group (14 min) than in the complete group (11 min), and resected specimen size and tumor size were larger in the incomplete group (36 mm and 14 mm)

than in the complete group (31 mm and 9 mm), but there was no statistically significant difference between the two groups. There were no statistically significant differences in location or circumference between the incomplete and complete groups.

Discussion

In the present study, we confirmed the feasibility and safety of the closure using FLEXLOOP following gastric ESD: the success rate of complete closure was 89%, and adverse events related to closure using FLEXLOOP were not reported.

Although closure methods using endoloops have been reported [11,17], an endoloop is a detachable snare that ligates the stalk of the polyp and is not a closure-dedicated device. Therefore, we developed a closure-dedicated device, FLEXLOOP, whose quality is no less than that of the endoloop and makes it a more simplified device.

Previously, the closure method using endoloop and clips has been reported [11,17], with closure times of 14 (range, 8–47) min and 15 (range, 4–60) min, respectively. A previous animal study on closure using FLEXLOOP showed that the time of closure was shorter than that using an endoloop [12]. The median closure time in this study was 11 (range, 8–43) min, suggesting that closure using FLEXLOOP is also faster than closure using the endoloop. FLEXLOOP consists of an independent outer sheath and nylon thread, which

allows flexible adjustment of the loop size and position, enabling shorter closure times owing to the ease of fixing the loop to the mucosal defect with clips.

The rate of complete closure in the present study was 89%, which was higher than the previous rates of closure using an endoloop of 73% [11] and 86% [17]. Based on these results, we conclude that closure using FLEXLOOP is superior to closure using an endoloop in terms of being a simplified, dedicated closure device, the time of closure, and the rate of complete closure.

As the global population ages, the incidence of cardiovascular diseases and arrhythmias has increased, and the number of patients receiving antithrombotic therapy is also increasing [18]. Previous studies have reported an extremely high rate of post-ESD bleeding in patients [19-22].

Recently, the BEST-J score has been a predictive model for bleeding risk following gastric ESD [6], with bleeding risks of 11.4% for high risk and 29.7% for very high risk. Therefore, an effective prophylactic treatment to prevent post-ESD bleeding for high-risk or very high-risk patients is desired. Although our study included patients at various risks of post-ESD bleeding, we were able to achieve a 0% rate of post-ESD bleeding. In the future, a large prospective study is required to confirm the efficacy of mucosal closure using FLEXLOOP with endoclips in high-risk and very high-risk patients.

As for the actual number of cases, assuming a post-ESD bleeding rate of 15% in patients with a high or very high BEST-J risk score, we hypothesized that the post-ESD bleeding rate could be reduced to 5% if mucosal closure using FLEXLOOP with endoscopic clips is performed. Based on the parameters $\alpha = 0.05$ (two-sided level) and power $(1-\beta) = 0.9$, a sample size calculation with a one arm binominal model required 89.

To prevent or reduce the risk of adverse events, several other closure methods for mucosal defects following gastric ESD have been reported, including closure using over-the-scope clip (OTSC) system (Ovesco Endoscopy AG, Tubingen, Germany) [8], closure using OverStich (Apollo Endosurgery Inc., Austin, Texas) [23], endoscopic hand suturing (EHS) [9], endoscopic ligation with O-ring closure (E-LOC) [24], closure using reopenable clip with anchor prongs (Boston Scientific, Marlborough, Massachusetts, USA) [25], and the clip-over-the-line method (ROLM) [26]. The closure technique using OTSC has a stronger grasping force than the other closure methods but has several problems, such as the possibility of involving other extraluminal organs, high cost, and limited size of the mucosal defect [27]. OverStich is a dedicated suture device produced by Apollo Endosurgery in the USA [23]; however, in Japan, it is only available at a few facilities and is difficult to use in general hospitals. Moreover, OverStich involves complicated and expensive procedures. EHS is a dedicated suture device that can be

domestically used, but it has a time-consuming suturing process (suture time of 49.5 min), involves technical difficulties, and requires expert-level skills [9]. However, in the present study, 46% of the closures were performed by nonexperts, and the success rate was 94%. In terms of cost, FLEXLOOP costs USD 46, which is more affordable than other devices, such as EHS, which costs USD 804, or OTSC, which costs USD 534. Hence, the closure using FLEXLOOP is simple and cost-effective and does not require special techniques.

E-LOC and ROLM are closure techniques that can be validated in general hospitals using existing endoscopic ligation devices or reopenable clips; however, the procedures seem to be relatively complicated and require a significant amount of procedure time to close within 60 min or 30 min, respectively.

In terms of closure outcome, the rates of complete closure were 91.7% (closure using OTSC), 100% (closure using OverStich), 97% (EHS), 97.9% (E-LOC), 100% (ROLM). The complete closure rate using FLEXLOOP was 89%, which is relatively lower than previous reports, but it is not generally comparable because of differences in endoscopists' skills, the number of participants, and evaluation methods.

Previous reports on the ulcer healing process have indicated that non-closed ulcers heal in approximately 8 weeks [28,29]. A previous study showed that closure using an endoloop enabled the mucosal defect to heal earlier [30], and another study examined the

healing process of EHS in a porcine model and found that closure of the mucosal defect promoted ulcer healing [31]. Therefore, closure of the mucosal defect potentially promotes ulcer healing. In this study, third-look endoscopy 4 or 5 weeks later revealed that the rate of the mucosal defect developing hearing stage was 64%. Thus, our findings are also more supportive of the results of previous studies, which have reported that closure of the mucosal defect suggests that ulcer healing can be promoted.

Although FLEXLOOP is a novel, simple, and dedicated closure device, it has some issues. A previous review article described mucosa-to-mucosa defect closure resulting in submucosal dead space (SDS) due to the thickness of the gastric wall, which has been a cause of early phase dehiscence [32]. In our study, the rate of sustained closure on PODs 5–7 was 20%, which has the potential due to SDS, but the rate of sustained closure on PODs 10–11 in previous report was 33% [24], which we believe is comparable with previous results. However, given the low sustained closure rate, we are now planning to improve the closure method using FLEXLOOP to reduce SDS.

Our study has some limitations. First, because this was a pilot study, the sample size was relatively small and there were few lesions in the upper third of the stomach. In general, the opportunity to encounter gastric neoplasia in the upper third is low [7], and to obtain more lesions in the upper third of the stomach, the total sample size must be

greater. Second, as the inclusion criteria in this pilot study were clinically diagnosed gastric neoplasia < 30 mm in size, it is unclear whether mucosal closure using FLEXLOOP with endoclips for lesions > 30 mm in size is feasible. It may be possible to enable closure using a combination of some FLEXLOOPs; however, further studies are required. Third, our study did not include lesions extending to the cardia or pyloric ring; therefore, the feasibility of closure using FLEXLOOP for these lesions will be confirmed in future clinical trials.

In conclusion, closure of mucosal defects using FLEXLOOP with clips is feasible and safe. Our technique using this new device can be an attractive option for easier approach to closing mucosal defects. However, further clinical studies to confirm that this technique can prevent delayed complications are warranted.

References

1. Ono H, Kondo H, Gotoda T et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001; 48: 225–229

2. Ono H, Hasuike N, Inui T et al. Usefulness of a novel electrosurgical knife, the insulation-tipped diathermic knife-2, for endoscopic submucosal dissection of early gastric cancer. Gastric Cancer 2008; 11: 47–52

3. Hasuike N, Ono H, Boku N et al. A non-randomized confirmatory trial of an

expanded indication for endoscopic submucosal dissection for intestinal-type gastric cancer (cT1a): The Japan Clinical Oncology Group study (JCOG0607). Gastric Cancer 2018; 21: 114–123

4. Takizawa K, Ono H, Hasuike N et al. A nonrandomized, single-arm confirmatory trial of expanded endoscopic submucosal dissection indication for undifferentiated early gastric cancer: Japan Clinical Oncology Group study (JCOG1009/1010). Gastric Cancer 2021; 24: 479–491

5. Suzuki H, Ono H, Hirasawa T et al. J WEB/EGC group. Long-term survival endoscopic resection for gastric cancer: Real-world evidence from a multicenter prospective cohort. Clin Gastroenterol Hepatol 2023; 21: 307–318.e2

6. Hatta W, Tsuji Y, Yoshio T et al. Prediction model of bleeding after endoscopic submucosal dissection for early gastric cancer: BEST-J score. Gut 2021; 70: 476–484.

7. Suzuki H, Takizawa K, Hirasawa T et al. Short-term outcomes of multicenter prospective cohort study of gastric endoscopic resection: 'Real-world evidence' in Japan. Dig Endosc 2019; 31: 30–39

8. Maekawa S, Nomura R, Murase T et al. Complete closure of artificial gastric ulcer after endoscopic submucosal dissection by combined use of a single over-the-scope clip and through-the-scope clips (with videos). Surg Endosc 2015; 29: 500–

504

9. Goto O, Oyama T, Ono H et al. Endoscopic hand-suturing is feasible, safe, and may reduce bleeding risk after gastric endoscopic submucosal dissection: A multicenter pilot study (with video). Gastrointest Endosc 2020; 91: 1195–1202

10. Kataoka Y, Tsuji Y, Hirasawa K et al. Endoscopic tissue shielding to prevent bleeding after endoscopic submucosal dissection: A prospective multicenter randomized controlled trial. Endoscopy 2019; 51: 619–627

11. Shiotsuki K, Takizawa K, Notsu A et al. Endoloop closure following gastric endoscopic submucosal dissection to prevent delayed bleeding in patients receiving antithrombotic therapy. Scand J Gastroenterol 2021; 56: 1117–1125

12. Nose Y, Takizawa K, Shiotsuki K et al. A novel, simple, and dedicated device for endoscopic mucosal defect closure. DEN Open 2022; 2: e98

13. Ono H, Yao K, Fujishiro M et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). Dig Endosc 2021; 33: 4–20.

14. Kato M, Uedo N, Hokimoto S et al. Guidelines for gastroenterological endoscopy in patients undergoing antithrombotic treatment: 2017 appendix on anticoagulants including direct oral anticoagulants. Dig Endosc 2018; 30: 433–440

15. Takizawa K, Oda I, Gotoda T et al. Routine coagulation of visible vessels may

prevent delayed bleeding after endoscopic submucosal dissection--An analysis of risk factors. Endoscopy 2008; 40: 179–183

16. Choi KD, Jung HY, Lee GH et al. Application of metal hemoclips for closure of endoscopic mucosal resection-induced ulcers of the stomach to prevent delayed bleeding. Surg Endosc 2008; 22: 1882–1886

17. Ego M, Abe S, Nonaka S et al. Endoscopic closure utilizing endoloop and endoclips after gastric endoscopic submucosal dissection for patients on antithrombotic therapy. Dig Dis Sci 2021; 66: 2336–2344.

18. Hallas J, Dall M, Andries A et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: Population based case-control study. BMJ 2006; 333: 726

19. Yoshio T, Nishida T, Kawai N et al. Gastric ESD under heparin replacement at high-risk patients of thromboembolism is technically feasible but has a high risk of delayed bleeding: Osaka University ESD Study Group. Gastroenterol Res Pract 2013; 2013: 365830

20. Ono S, Fujishiro M, Yoshida N et al. Thienopyridine derivatives as risk factors for bleeding following high risk endoscopic treatments: Safe Treatment on Antiplatelets (STRAP) study. Endoscopy 2015; 47: 632–637

21. Sato C, Hirasawa K, Koh R et al. Postoperative bleeding in patients on

antithrombotic therapy after gastric endoscopic submucosal dissection. World J Gastroenterol 2017; 23: 5557–5566

22. Igarashi K, Takizawa K, Kakushima N et al. Should antithrombotic therapy be stopped in patients undergoing gastric endoscopic submucosal dissection? Surg Endosc 2017; 31: 1746–1753

23. Kantsevoy SV, Bitner M, Mitrakov AA et al. Endoscopic suturing closure of large mucosal defects after endoscopic submucosal dissection is technically feasible, fast, and eliminates the need for hospitalization (with videos). Gastrointest Endosc 2014; 79: 503–507

24. Nishiyama N, Kobara H, Kobayashi N et al. Efficacy of endoscopic ligation with O-ring closure for prevention of bleeding after gastric endoscopic submucosal dissection under antithrombotic therapy: A prospective observational study. Endoscopy 2022; 54: 1078–1084.

25. Nishiyama N, Matsui T, Nakatani K et al. Novel strategy of hold-and-drag clip closure with mantis-like claw for post-gastric endoscopic submucosal dissection defect of <30 mm. Endoscopy 2023; 55: E1244–E1245.

26. Nomura T, Sugimoto S, Temma T et al. Reopenable clip-over-the-line method for closing large mucosal defects following gastric endoscopic submucosal dissection: Prospective feasibility study. Dig Endosc 2023; 35: 505–511.

27. Kobara H, Mori H, Nishiyama N et al. Over-the-scope clip system: A review of 1517 cases over 9 years. J Gastroenterol Hepatol 2019; 34: 22–30

28. Kakushima N, Fujishiro M, Kodashima S et al. Histopathologic characteristics of gastric ulcers created by endoscopic submucosal dissection. Endoscopy 2006; 38: 412–415

29. Niimi K, Fujishiro M, Goto O et al. Prospective single-arm trial of two-week rabeprazole treatment for ulcer healing after gastric endoscopic submucosal dissection. Dig Endosc 2012; 24: 110–116

30. Lee BI, Kim BW, Kim HK et al. Routine mucosal closure with a detachable snare and clips after endoscopic submucosal dissection for gastric epithelial neoplasms: A randomized controlled trial. Gut Liver 2011; 5: 454–459

31. Akimoto T, Goto O, Sasaki M et al. Endoscopic suturing promotes healing of mucosal defects after gastric endoscopic submucosal dissection: Endoscopic and histologic analyses in in vivo porcine models (with video). Gastrointest Endosc 2020; 91: 1172–1182.

32. Nomura T, Sugimoto S, Temma T et al. Suturing techniques with endoscopic clips and special devices after endoscopic resection. Dig Endosc 2023; 35: 287–301.

Figure legends

Figure 1: Combination of a single-channel endoscope and FLEXLOOP (Hakko Co., Ltd., Nagano, Japan). The FLEXLOOP comprises a nylon thread and an outer sheath. The nylon thread is joined with silicone rubber and stainless steel.

Figure 2a: Esophagogastroduodenoscopy reveals a mucosal defect (> 40 mm in diameter) following gastric endoscopic submucosal dissection. **b:** The first clip is inserted into the edge of the mucosal defect along with the nylon thread of FLEXLOOP. **c:** Multiple clips are circumferentially anchored along the mucosal defect. **d:** The mucosal defect is closed by tightening the loop and pushing the outer sheath; subsequently, the mucosal defect is completely closed.

Table 1. Baseline characteristics of patients and lesions

Characteristics	n=35
Age, years, median (range)	72 (47–87)
Sex, n (%)	
Men	27 (77)
Women	8 (23)
Comorbidities, n (%)	
Hypertension	14 (40)
Malignancy	10 (29)
Liver disease	3 (9)
Arrhythmia	2 (6)
Ischemic heart disease	2 (6)
Diabetes mellitus	2 (6)
Cerebrovascular disease	1 (3)
Antithrombotic agents, n (%)	
Administered	7 (20)
Not administered	28 (80)
Location, n (%)	
Upper third	4 (11)
Middle third	16 (46)
Lower third	15 (43)

Circumference, n (%)	
Greater curvature	12 (34)
Posterior wall	11 (32)
Lesser curvature	6 (17)
Anterior wall	6 (17)
Gross type, n (%)	
0–IIc	24 (69)
0–IIa	5 (14)
0–IIb	5 (14)
0–IIa + IIc	1 (3)

Table 2. Outcomes of endoscopic submucosal dissection and histology

	n=35
En bloc resection, n (%)	35 (100)
R0 resection, n (%)	33 (94)
Curative resection, n (%)	33 (94)
Procedure time, median (range), min	33 (12–107)
Size of resected specimen, median (range), mm	32 (22–56)
Size of the tumor, median (range), mm	10 (3–35)
Intraoperative perforation, n (%)	0 (0)
Delayed perforation, n (%)	0 (0)
Histology, n (%)	
Diagnosis	
Adenocarcinoma	35 (100)
Tumor depth	
Mucosa	32 (91)
SM1	1 (3)
SM2	2 (6)
Ulceration	
Absent	35 (100)
Differentiation	
Differentiated	30 (86)

Undifferentiated	5 (14)
Lymphovascular invasion	
Present	1 (3)
Absent	34 (97)

1 **Table 3.** Outcomes of closure using FLEXLOOP with endoclips

2

	n=35
Completeness of closure using FLEXLOOP and endoclips, n (%)	
Complete	31 (89)
Incomplete	4 (11)
Failure	0 (0)
Procedure time for closure, median (range), min	11 (8–30)
Number of FLEXLOOP, median (range)	1 (1–2)
Number of endoclips, median (range)	10 (8–17)
Adverse events related to closure using FLEXLOOP	0 (0)
Endoscopist degree, n (%)	
Expert	19 (54)
Nonexpert	16 (46)
Sustained closure rate on PODs 5–7	
Sustained	7 (20)
Partially	22 (63)
Unsustained	6 (17)
Complete closure success rate related to location, n (%)	
Upper third	3/4 (75)
Middle third	14/16 (88)

Lower third	14/15 (93)
Complete closure success rate related to circumference, n (%)	
Greater curvature	10/12 (83)
Posterior wall	10/11 (91)
Lesser curvature	5/6 (83)
Anterior wall	6/6 (100)
Sustained closure rate on PODs 5–7 related to location, n (%)	
Upper third	1/4 (25)
Middle third	3/16 (19)
Lower third	3/15 (20)
Sustained closure rate on PODs 5–7 related to circumference, n (%)	
Greater curvature	3/12 (25)
Posterior wall	2/11 (18)
Lesser curvature	0/6 (0)
Anterior wall	2/6 (33)
Post-ESD bleeding, n (%)	0 (0)
Best-J risk stratification, n (%)	
Low risk	27 (77)
Intermediate	5 (14)
High	3 (9)
Closure site at approximately 4 or 5 weeks later, n (%)	

Hearing stage scar formation	21/33 (64)
Closure opened	9/33 (27)
Remained closure	3/33 (9)

PODs, postoperative days

Table 4. Comparison of closure outcomes using FLEXLOOP with endoscopic clips between expert and nonexpert

	Expert n=19	Nonexpert n=16	P value
Completeness of closure using FLEXLOOP and endoclips, n (%)			
Complete	16 (84)	15 (94)	
Incomplete	3 (16)	1 (6)	0.60
Failure	0 (0)	0 (0)	
Procedure time for closure, median (range), min	12 (8–30)	9 (8–15)	0.04
Size of the tumor, median (range), mm	11(4–35)	8 (4–24)	0.09
Location, n (%)			
Upper third	3 (16)	1 (6)	
Middle third	9 (47)	7 (44)	1.00
Lower third	7 (37)	8 (50)	
Circumference, n (%)			
Greater curvature	7 (37)	5 (31)	
Posterior wall	5 (26)	6 (38)	
Lesser curvature	4 (21)	2 (13)	1.00
Anterior wall	3 (16)	3 (18)	

Sustained closure rate on PODs 5–7			
Sustained	1 (5)	6 (38)	0.03
Partially	14 (74)	9 (56)	0.30
Unsustained	4 (21)	1 (6)	0.35
Complete closure success rate related to location, n (%)			
Upper third	2/3 (67)	1/1 (100)	1.00
Middle third	8/9 (88)	6/7(86)	1.00
Lower third	6/7 (86)	8/8 (100)	0.47
Complete closure success rate related to circumference, n (%)			
Greater curvature	6/7 (86)	4/5 (80)	1.00
Posterior wall	4/5 (80)	6/6 (100)	0.46
Lesser curvature	3/4 (75)	2/2 (100)	1.00
Anterior wall	3/3 (100)	3/3 (100)	1.00
Sustained closure rate on PODs 5–7 related to location, n (%)			
Upper third	0/3 (0)	1/1 (100)	0.40
Middle third	0/9 (0)	3/7 (43)	0.06
Lower third	1/7 (14)	2/8 (25)	1.00

Sustained closure rate on PODs 5–7 related to circumference, n (%)			
Greater curvature	1/7 (14)	2/5 (40)	1.00
Posterior wall	0/5 (0)	2/6 (33)	0.45
Lesser curvature	0/4 (0)	0/2 (0)	1.00
Anterior wall	0/3 (0)	2/3 (67)	0.40

1 PODs, postoperative days
2

Table 5. Risk factors for incomplete closure using FLEXLOOP with endoscopic clips

	Incomplete n=4	Complete n=31	P value
Age, years, median (range)	72 (63–81)	72 (55–84)	1.00
Sex, n (%)			
Men	3 (75)	24 (77)	1.00
Women	1(25)	7 (23)	
Location, n (%)			
Upper third	1 (25)	3 (10)	0.39
Middle third	2 (50)	14 (45)	1.00
Lower third	1 (25)	14 (45)	0.62
Circumference, n (%)			
Greater curvature	2 (50)	10 (32)	0.59
Posterior wall	1 (25)	10 (32)	1.00
Lesser curvature	1 (25)	5 (16)	0.55
Anterior wall	0 (0)	6 (20)	1.00
Endoscopist degree, n (%)			
Expert	3 (75)	16 (52)	0.60
Nonexpert	1 (25)	15 (48)	
Procedure time, median (range), min	14 (9–30)	11(8–21)	0.62

Number of endoclips, median (range)	10 (9–17)	10 (8–17)	0.62
Size of resected specimen, median (range), mm	36 (35–56)	31(20–52)	0.60
Size of the tumor, median (range), mm	14 (3–35)	9(4–30)	0.60

Supplementary Video 1

Complete closure of the mucosal defect following gastric endoscopic submucosal dissection using FLEXLOOP and multiple clips.