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Improved outcomes of endoscopic treatment for delayed perforation following endoscopic submucosal dissection for gastric epithelial neoplasms

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Abstract:

Background and study aim

Emergency surgery is usually required in patients with delayed perforation after gastric endoscopic submucosal dissection (ESD); however, cases of successful endoscopic treatment have been recently reported. Here, we elucidated the usefulness of endoscopic intervention for patients with delayed perforation.

Patients and methods

Patients who underwent gastric ESD from 2005–2022 were assessed for eligibility. Delayed perforation was defined as no intraprocedural perforation after the ESD but subsequent development of peritoneal irritation and free air on the computed tomography scan. Participants were divided into early- and late-period groups based on the time (October 2015) of implementation of the polyglycolic acid (PGA) sheet and the over-the-scope clip (OTSC) in clinical practice. We evaluated the changes in the incidence of required surgery.

Results

Among the 5,048 patients who underwent gastric ESD, delayed perforation occurred in 28 patients (0.6%, 95% confidence interval [CI]: 0.4%–0.8%). The incidence of delayed perforation did not differ significantly between the early- and late-period groups (0.5% vs. 0.6%). The proportion of patients who underwent surgery was significantly smaller in the late-period group than in the early-period group (54% vs. 13%, odds ratio: 0.14 [95% CI: 0.02–0.83], p = 0.042); this was confirmed by multivariate analysis (adjusted odds ratio: 0.04 [95% CI: 0.002–0.9, p = 0.043) after adjustment for age, sex, Charlson's comorbidity index, tumor location, and size.

Conclusions

Endoscopic intervention using PGA sheets and OTSC was associated with a low incidence of required surgery for delayed perforation after gastric ESD and is recommended.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is a minimally invasive treatment for gastric epithelial neoplasms and is widely performed worldwide [1, 2]. Delayed perforation is a life-threatening adverse event in ESD. Previously, 43%–83% of patients with delayed perforation in gastric ESD required surgery [3-5]. However, many case reports have demonstrated that patients with delayed perforation in gastric ESD could avoid surgery by undergoing endoscopic closure of the perforation [6-11]. In those reports, polyglycolic acid (PGA) sheets and over-the-scope clip (OTSC) were used for the endoscopic closure of the delayed perforation [6, 7, 10]. We hypothesized that using PGA sheets and OTSC could offer a successful alternative to surgery. Therefore, in this study, we aimed to clarify the incidence of delayed perforation after gastric ESD and the effect of endoscopic intervention on the clinical outcomes of these patients.

PATIENTS AND METHODS

Study design and participants

This was a single-center, retrospective observational study conducted at Osaka International Cancer Institute. Patients provided written informed consent for the use of medical information in clinical studies as a component of providing comprehensive consent. The study protocol was approved by the institutional review board (IRB No. 23111).

The ESD database in our department and the hospital's electronic medical record were used to identify patients with delayed perforation and to assess their outcomes. In addition, to avoid missing data, electronic searches were supplemented with verbal and E-

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mail interviews with endoscopists who were involved in the ESD procedures and patient management.

Patients who underwent ESD for gastric epithelial neoplasms between January 2005 and December 2022 were assessed for eligibility. The onset of delayed perforation was reported to be within 24–72 h [3-5, 9, 12]. However, these reports were retrospective studies, and the accurate onset time of delayed perforation was poorly clarified. Therefore, patients who underwent computed tomography (CT) scans within 1 month after gastric ESD were initially screened to avoid missing the patients with delayed perforation. Among them, patients were excluded if they met any of the following criteria: (1) had intraprocedural perforation; (2) did not experience subsequent peritoneal irritation during the post-ESD period; (3) had no free air in the CT scan; or (4) had other causes of the delayed perforation besides ESD.

The study participants were divided into early- and late-period groups based on October 1, 2015, because the PGA sheets and OTSC were introduced in our clinical practice at that time.

ESD procedure

ESD was performed by experienced board-certified endoscopists or their supervised endoscopy fellows. Carbon dioxide (CO_2) was used for endoscopic insufflation. An insulated-tip knife (KD-610L or KD-611L; Olympus Corporation, Tokyo, Japan), a needle-typed knife (FlushKnife, DK 2620J; FUJIFILM Medical Co., Ltd., Tokyo, Japan), or a scissor type knife (Clutch Cutter, DP2618DT; FUJIFILM Medical Co., Ltd.) was used with an electrosurgical generator (ICC-200, VIO 300D, or

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VIO 3; ERBE, Tübingen, Germany, or PSD-60; Olympus Corporation). Following the injection of 0.4% hyaluronic acid (MucoUp; Boston Scientific Japan K.K., Tokyo, Japan) with or without 0.001% epinephrine (Bosmin; Daiichi Sankyo Co., Ltd., Tokyo, Japan) into the submucosa, mucosal incision and submucosal dissection were performed using the standard strategy [13]. During the procedure, minor bleeding from a thin vessel was cauterized with the electrosurgical knife, and major bleeding from a thick vessel was managed with hemostatic forceps (Radial Jaw 4 Hot Biopsy Forceps; Boston Scientific Japan K.K., or Coagrasper, FD-410LR; Olympus Corporation) using a soft coagulation mode. After resection, any exposed vessels on the post-resection ulcer were cauterized using these hemostatic forceps. The endoscope was removed after careful observation to ensure that no intraoperative perforation was found in the post-ESD ulcer.

Perioperative management

Immediately after ESD, abdominal palpation was performed to assess whether there were any findings suspicious of intraoperative perforation, and simple X-ray or CT scans examinations were not routinely performed. Water intake was initiated on postoperative day (POD) 0 after confirming the absence of adverse events such as perforation or bleeding. A blood test was conducted on POD 1. If the patient remained symptom-free, food intake was initiated on POD 2, and the patient was discharged on POD 4. Second-look endoscopy was not routinely performed unless there was a sign of delayed adverse events. Perioperative management of antithrombotic agents followed the guidelines issued by the Japan Gastroenterological Endoscopy Society [14, 15].

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Management after detection of delayed perforation

When delayed perforation was suspected, an abdominal CT scan was initially performed. When the free air was confirmed in the peritoneal space, the management of the delayed perforation was decided in discussion among the endoscopic team and the surgeons. An emergency endoscopy was performed under CO_2 insufflation if (1) the patient's condition was stable, and (2) peritonitis was localized within a quadrant of the abdomen. If a perforation hole was identified during the emergency endoscopy, endoscopic closure was attempted. However, if a perforation hole was not confirmed, patients were followed up carefully under conservative treatment, such as placement of a nasogastric tube and administration of intravenous antibiotics. Surgical operation was indicated when peritoneal signs were observed throughout the abdomen or if peritonitis did not improve with conservative treatment or endoscopic intervention.

PGA sheet placement

In placing PGA sheets (Neoveil 015; Gunze Medical Ltd., Osaka, Japan) for the closure of delayed perforation, a fibrin glue (Beriplast P Combi-Set; CSL Behring Pharma, Tokyo, Japan) was used to fix the PGA sheet [7]. Beriplast included solution A (fibrinogen) and solution B (thrombin). After detecting the perforation hole, a 100 × 50 mm PGA sheet was cut into small pieces (approximately 15 × 7 mm to 20 × 20 mm), inserted through the working channel using hot-biopsy forceps (FD-1L-1; Olympus Corporation), and placed onto the perforation hole. After applying several sheets, solution A was applied to the PGA sheets using an endoscopic catheter (Fine Jet; Top

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Corporation, Tokyo, Japan), and solution B (thrombin) was sprayed over the PGA sheets using another endoscopic catheter.

OTSC closure

The OTSC system (Ovesco Endoscopy, Tübingen, Germany) comprises an applicator cap, a clip, and a handle. The 9-mm “t” type OTSC, which has short and sharp teeth, was commonly used in this study. After detecting the delayed perforation hole, the endoscope was withdrawn, and the OTSC was mounted. The tissues around the perforation hole were suctioned into the applicator cap, and the clip was deployed. If an insufficient amount of tissue was pulled into the cap, a grasping forceps or a double grasping forceps (Twin Grasper; Ovesco Endoscopy, Tübingen, Germany) was used to retract the tissue.

Variables and definition

The body mass index was calculated as weight in kilograms divided by height in meters squared. Comorbidity was considered present based on the definition in the Charlson comorbidity index. The prognostic nutritional index was calculated using the formula: 10 × serum albumin (g/dL) + 0.005 × lymphocytes/μL. Tumor characteristics were described according to the Japanese classification of gastric carcinoma [16].

Outcomes

Delayed perforation was defined as the absence of intraoperative perforation or abdominal symptoms immediately after ESD and the subsequent appearance of

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peritoneal irritation with free air outside the gastric wall on a CT scan. The primary outcome was the change in the incidence of surgery for delayed perforation between the early and late periods.

Statistical analysis

All continuous variables are reported as the median (interquartile range [IQR]), and all categorical variables are summarized as numbers (frequencies). To compare clinic al variables between the early and late periods, we used Fisher's exact test for categorical variables and Mann–Whitney U test for the continuous variables. As an exploratory analysis, multivariate logistic regression analysis was performed to test the independence of association between the periods and the incidence of surgery. *P*-values < 0.05 were considered statistically significant. All analyses were performed using the EZR software package v. 1.55 (Saitama Medical Center, Jichi Medical University, Tochigi, Japan).

RESULTS

Incidence of delayed perforation

Among the 5,048 patients who underwent ESD for gastric neoplasms between January 2005 and December 2022, 444 patients had CT scans within 1 month after ESD. After excluding 300 patients who received CT scans for indications other than peritoneal irritation and 55 who had intraprocedural perforation, 89 patients had CT scans because of symptoms of peritoneal irritation after ESD. Of these, 61 patients were excluded due to the absence of free air in the abdominal cavity. Verbal and E-mail interviews with all endoscopists involved in ESD procedures during the study period revealed that no other

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patients developed delayed perforation. Therefore, delayed perforation developed in 28 patients (0.6%, 95% confidence interval [CI]: 0.4%–0.8%, Figure 1). The incidence of delayed perforation was similar between the early (13 of 2,616 patients [0.5%, 95% CI: 0.3%–0.8%]) and late (15 of 2,432 patients [0.6%, 95% CI: 0.3%–1.0%]) period groups.

The background characteristics of patients with delayed perforation are presented in Table 1. The median age of these patients was 69 years (IQR: 63–81 years), and 16 patients (57%) were men. Regarding the location, delayed perforation was most frequently observed in the upper third of the stomach (43%). No significant difference was observed in the background characteristics of the study participants and lesions between the early- and late-period groups.

Difference in clinical outcomes of the patients with delayed perforation between the early and late period

Clinical outcomes of the patients with delayed perforation are presented in Table 2 and Figure 2. The median time until diagnosis of peritonitis after the ESD procedure was 14 h (IQR: 9–20 h), and the maximum time was 46 h.

In patients who developed delayed perforation in the early-period group (n = 13), only two (15%) received emergency endoscopy, whereas 12 (80%) of 15 patients received emergency endoscopy in the late-period group (p = 0.002). In the early-period group, six patients underwent surgical operation without receiving emergency endoscopy. Among them, four received surgical operation several hours after delayed perforation was identified, and two received surgery the day after conservative treatment with intravenous antibiotics failed to improve the peritonitis. One patient

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received emergency endoscopy and endoscopic clipping but eventually underwent surgery the next day as the peritonitis was not improved. In the late-period group, one patient underwent surgical operation without receiving an emergency endoscopy several hours after delayed perforation was identified, 12 received emergency endoscopy, eight received endoscopic intervention (endoclip in one, PGA sheet in three, and OTSC in four), one of whom underwent surgery the next day because of persistent peritonitis symptom (Figure 2). Among the 28 patients with delayed perforation, 27 (96%) patients started oral intake and were discharged without additional adverse events. One (4%) patient (an 83-year-old man) who underwent surgery without an emergency endoscopy could not start oral intake because of impaired swallowing function due to disuse syndrome after surgery. He was transferred to another hospital for rehabilitation of swallowing function 37 days after ESD.

Accordingly, the proportion of the patients whose delayed perforation was managed by endoscopic intervention was significantly higher in the late-period group than in the early-period group (0% [0 of 13 patients] vs. 47% [7 of 15 patients], Table 2). The success rate of endoscopic treatment in cases of detected perforation was 85.7% (6/7 patients) in the late-period group (Figure 2). The number of patients who required surgery was lower in the late-period group than in the early-period group (13% [2 of 15 patients] vs. 54% [7 of 13 patients], $p = 0.007$, Table 2). Over time, OTSC was more commonly used than the PGA sheet for endoscopic intervention (Table 3, Figures 3 and 4). Inflammatory parameters such as the incidence of fever (> 37.6°C), maximum white blood cell count, C-reactive protein levels, and time to recovery of these values were similar in early and late periods. The median (IQR) time to start food intake after ESD

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(6 [5–7] days vs. 8 [7–13] days, p = 0.021) and the period of hospitalization (11 [9–13] days vs. 17 [14–25] days, p = 0.001) were significantly shorter in the late-period group than in the early-period group (Table 2).

Univariate analysis revealed that the late period was significantly associated with a lower incidence of surgery for delayed perforation (odds ratio [OR]: 0.14, 95% CI: 0.02–0.83, p = 0.042, Table 4). Even after adjusting for age, sex, comorbidity, tumor location, and size by multivariate logistic regression analysis, the significant association between the low incidence of surgery and the period remained (adjusted OR: 0.04, 95% CI: 0.002–0.9, p = 0.043).

DISCUSSION

In this study, we demonstrated that, after implementing the PGA sheet and OTSC, emergency endoscopy was more frequently performed in patients with delayed perforation after gastric ESD, endoscopic intervention was attempted when possible, and the number of patients who required surgery was significantly reduced.

Delayed perforation in gastric ESD is rare, with an incidence ranging from 0.1%–0.6% [3-5, 9, 12]. The risk factors include older age, gastric tube reconstruction after esophagectomy, and procedures performed on the lesser curvature or the upper third of the stomach [3, 4, 9, 12]. The background characteristics of our study participants were consistent with those in these reports. We encountered no cases of gastric tube reconstruction after esophagectomy; however, we observed two cases of remnant stomach after distal gastrectomy. Regarding the mechanism of delayed perforation, Hanaoka et al. suggested an association with ischemic change caused by electrical cautery during ESD or

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repeated coagulation [3]. Yamamoto et al. demonstrated an association between the average duration of electrical cautery needed for hemostasis and the areas that developed delayed perforation, with significantly longer durations observed in the areas that developed delayed perforation than the non-delayed perforation areas (9 s vs. 3.5 s) [5].

Delayed perforation differs from intraoperative perforation in that it often involves a larger perforation size, and the tissues around the perforation site are more friable, which can make closure with conventional endoclips challenging [17]. A PGA sheet is an absorbable reinforcement material that, when used in combination with the fibrin glue, acts as a scaffold for tissue generation and promotes the healing of the perforation site [18]. Takimoto et al. reported three cases of delayed perforation in gastric ESD that were successfully managed without surgery using PGA sheets for endoscopic closure [7]. OTSC is a novel endoscopic device that enables full-thickness closure of the digestive tract [19]. Voermans et al. investigated the efficacy of OTSC in gastrointestinal perforation and demonstrated a successful endoscopic closure rate of 89% (32 of 36 cases), particularly achieving a 100% (6 of 6 cases) rate in the stomach [20].

Previous studies have suggested that the perforation size is associated with the likelihood of avoiding surgery in patients with delayed perforation in gastric ESD [9, 12]. Yamamoto et al. reported that all (n = 5) patients with delayed perforation, in which the perforation size was less than 5 mm, could avoid surgery [9]. Kim et al. reported that a small perforation size (< 1 cm) was significantly associated with avoidance of surgery. In our study, endoscopic closure was technically successful in all (n = 9) patients whose perforation size was ≤ 1 cm (Table 3). However, even after the successful endoscopic closure, two patients required surgery because of unimproved peritonitis. Our results

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underscore the importance of careful monitoring of the patient's condition to avoid missing the optimal timing of surgery after the successful endoscopic closure.

Despite the technical advancements in gastric ESD, the incidence of delayed perforation was similar between the early- and the late-period groups in this study. Thus, monitoring and managing delayed perforation remains important after gastric ESD. A recent systematic review by Yamamoto et al. indicated that endoscopic treatment, including clip closure, PGA sheet placement, or OTSC, is considered for delayed perforation when the peritonitis is absent or localized [17]. Our results demonstrated that among the nine patients who were treated with PGA sheet or OTSC, seven recovered without requiring surgery. Regarding the selection of PGA sheet or OTSC for the closure of the perforation, recently OTSC was initially used in our hospital. The advantage of using OTSC over PGA sheets is the robust closure of the perforation. The OTSC mechanically enables full-thickness closure, while PGA sheets merely act as a scaffold for tissue generation. In contrast, PGA sheet may be useful in perforation where the surrounding muscle tissue is fragile, or as a complement to clip/OTSC closure where microperforation remains after clip/OTSC placement.

It has been reported that intra-abdominal free air of no clinical significance (so-called "transmucosal air leakage") can be detected on abdominal CT scan after gastric ESD in up to 38% of cases [21, 22]. In addition, it could be difficult to differentiate between peritoneal irritation due to post-ESD coagulation syndrome and true delayed perforation. Therefore, patients with post-ESD coagulation syndrome with "transmucosal air leakage" may have been included as "delayed perforation" in this study. In fact, among the 14 patients diagnosed with delayed perforation on the CT scan, the perforation hole

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was not confirmed during the emergency endoscopy in six patients and all the patients recovered conservatively without surgical or endoscopic intervention (Figure 2). The results suggest the usefulness of emergency endoscopy to confirm delayed perforation and determine the need for endoscopic/surgical intervention.

This study has several strengths. First, it includes the largest number of cases of delayed perforation among studies conducted to date [3-5, 9, 12]. Additionally, we mitigat ed selection bias by extracting a list of patients who underwent CT scan within 1 month after gastric ESD from the electronic medical records. However, this study also has some limitations. First, this was a single-center, retrospective study conducted in a high-volume center; thus, the reproducibility in general hospitals needs to be confirmed. Second, although the number of cases was relatively large, considering the low incidence of delayed perforation in gastric ESD, the number of cases remained insufficient to draw reliable conclusions. Third, patients who did not receive a CT scan for delayed perforation and who developed delayed perforation more than 1 month after ESD were missed. Although the risk of recall bias remains, oral and e-mail interviews were conducted with all endoscopists involved in patient management to minimize this problem. Fourth, the availability of the closure device and technique may differ from other countries. The PGA sheet may be unavailable outside Japan, and endoscopic vacuum therapy [23] is rarely performed in Japanese practice. Although the method of closure may differ, we believe the importance of early endoscopic evaluation and endoscopic intervention at the site of delayed perforation is the same. Fifth, the time acclimatization of the endoscopists for management of delayed perforation may affect the length of time taken to resume oral intake, the length of hospitalization, and the indication of emergency endoscopy.

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However, the low incidence of surgery for delayed perforation in the late period cannot be explained by endoscopists' habituation. Even if the emergency endoscopy was performed and the delayed perforation was identified in the early-period, the patients could not avoid surgery because no endoscopic intervention method was available. We believe the endoscopic intervention using PGA sheets and OTSC offers a successful alternative to surgery. Despite these limitations, our study provides meaningful insights into the management of delayed perforation in gastric ESD. Conducting a large-scale, multi-center study would be useful to validate our results.

In conclusion, the implementation of endoscopic intervention using PGA sheets and OTSC was associated with a low incidence of surgery for delayed perforation in patients after gastric ESD. An emergency endoscopy and endoscopic intervention are recommended for such patients when they have stable clinical conditions and localized peritonitis.

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401 **FIGURE LEGENDS**

402 **Figure 1.** Selection flow of the study participants. *ESD: Endoscopic submucosal*
403 *dissection, CT: Computed tomography*.

404

405 **Figure 2.** Clinical outcomes of the patients with delayed perforation. *PGA: Polyglycolic*
406 *acid, OTSC: Over-the-scope clip.*

407

408 **Figure 3.** Endoscopic images of the case of delayed perforation treated using a
409 polyglycolic acid (PGA) sheet. (a) A 20-mm tumor located in the greater curvature of
410 the upper body of the operated stomach after distal gastrectomy by Billroth Ⅰ
411 anastomosis. (b) The tumor was removed by endoscopic submucosal dissection (ESD)
412 without intraoperative perforation. (c) The patient had epigastric pain 1.5 h after ESD.
413 Computed tomography showed free air. (d) Endoscopy revealed a 5-mm muscle defect
414 in the post-ESD ulcer (yellow head). (e) The perforation was closed using a PGA sheet
415 (yellow head). (f) After 2 months, the post-ESD ulcer was healed, including the
416 perforation.

417

418 **Figure 4.** Endoscopic images of the case of delayed perforation treated using an over-the-
419 scope clip (OTSC). (a) A tumor located in the greater curvature of the upper body of the
420 operated stomach after distal gastrectomy by Billroth Ⅰ anastomosis. The tumor was
421 unclear in the biopsy in the previous endoscopic examination. Thus, the marking was
422 performed around the biopsy scar. (b) The tumor was removed by endoscopic submucosal
423 dissection (ESD) without intraoperative perforation. (c) The patient had epigastric pain 13

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424 h after ESD. Computed tomography showed free air. (d) Endoscopy revealed a 5-mm
425 muscle defect in the post-ESD ulcer (yellow head). (e) The perforation was closed using
426 an OTSC. (f) After 2 months, the post-ESD ulcer healed, including the perforation.
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429 **Table 1. Characteristics of the patients and lesions with delayed perforation**

Clinical characteristics	**Total** n = 28	**Early period** n = 13	**Late period** n = 15	***P*-value**
Age, years	69 (63–81)	68 (65–80)	71 (60–82)	0.945
Sex				0.276
Male	16 (57)	9 (69)	7 (47)	
Female	12 (43)	4 (31)	8 (53)	
Body mass index, kg/m^2	22 (20–24)	23 (21–24)	22 (19–23)	0.170
Comorbidity				0.460
Present	17 (61)	9 (69)	8 (53)	
Absent	11 (39)	4 (31)	7 (47)	
Preoperative white blood cell, μL	5635	5640	5630	0.254
Preoperative C-reactive protein, mg/dL*	0.05	0.12	0.04	0.344
Serum albumin, g/dL†	4.2 (4.0–4.4)	4.3 (4.0–4.4)	4.2 (4.0–4.4)	0.922
Prognostic nutritional index†	44 (40–45)	43 (41–45)	44 (40–45)	0.905
Operated stomach				0.484
No	26 (93)	13 (100)	13 (87)	
Yes	2 (7)	0	2 (13)	

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Longitudinal location				0.082
Upper	12 (43)	7 (54)	5 (33)	
Middle	8 (29)	1 (7.7)	7 (47)	
Lower	8 (29)	5 (38)	3 (20)	
Circumferential location				0.720
Anterior wall	8 (29)	4 (31)	4 (27)	
Posterior wall	5 (18)	3 (23)	2 (13)	
Greater curvature	7 (25)	2 (15)	5 (33)	
Lesser curvature	8 (29)	4 (31)	4 (27)	
Endoscopic size, mm	16 (12–30)	15 (12–30)	16 (12–28)	0.871
Ulceration/scar				1.000
Present	6 (21)	3 (23)	3 (20)	
Absent	22 (79)	10 (77)	12 (80)	
Number of lesions				0.852
1	20 (71)	9 (69)	11 (73)	
2	3 (11)	2 (15)	3 (20)	
3	5 (18)	2 (15)	1 (7)	
Main ESD device				0.173
Insulated-tip knife	21 (75)	11 (84)	10 (67)	
Needle-typed knife	6 (21)	1 (7.7)	5 (33)	
Scissor type knife	1 (4)	1 (7.7)	0	
Fibrosis during procedure	8 (29)	3 (23)	5 (33)	0.696
Present	20 (71)	10 (77)	10 (67)	
Absent				

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Procedure time (from initial scope insertion to the last withdrawal), min	153 (116–211)	137 (86–185)	166 (130–217)	0.254

Data are presented as the median (interquartile range) or n (%). *ESD: Endoscopic submucosal dissection.* *Three patients were excluded in the early-period group because of the lack of data. †One patient was excluded in the early-period group because of the lack of data.

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434 **Table 2. Clinical outcomes of delayed perforation**

	Total n = 28	**Early period** n = 13	**Late period** n = 15	***P*-value**
Time until peritonitis was identified after ESD, hours	14 (9–20)	14 (10–21)	6 (13–18)	0.650
Fever (≥ 37.6℃)	23 (82)	10 (77)	13 (87)	0.639
Maximum white blood cell, μL	11855	11760	11950	0.363
Maximum C-reactive protein, mg/dL	14.9	15.7	14.1	0.156
Emergency endoscopy after delayed perforation	14 (50)	2 (15)	12 (80)	0.002
Final treatment for delayed perforation				0.007
Conservative treatment	12 (43)	6 (46)	6 (40)	
Endoscopic treatment	7 (25)	0	7 (47)	
Surgical operation	9 (32)	7 (54)	2 (13)	
Time until white blood cell decrease, POD	1.5 (1–2)	2 (1–2)	1 (1–2.5)	1.000
Time until C-reactive protein decrease, POD	3 (2–3)	2 (2–3)	3 (2–3)	0.238
Time to resume oral intake, POD	7 (6–8)	8 (7–13)	6 (5–7) *	0.021
Length of hospitalization, days	14 (11–17)	17 (14–25)	11 (9–13) *	0.001

435 Data are presented as the median (interquartile range) or n (%). *One patient was
436 excluded because of an inability to start oral intake and transferred to a different
437 hospital. *ESD: Endoscopic submucosal dissection, POD: Postoperative day.*

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438 **Table 3** Characteristics and clinical outcomes of nine patients with delayed perforation treated by endoscopic closure

Period (year)	Age, year	Sex	Longitudinal location	Circumferential location	Endoscopic tumor size, mm	Time until peritonitis was identified after ESD, hours	Perforation size, mm	Endoscopic treatment for delayed perforation	Surgical operation after endoscopic closure	Length of hospitalization, day
Early (2011)	68	Male	U	Posterior wall	10	17	5	Clipping	Present	45
Late (2015)	66	Male	U	Greater curvature	20	1.5	5	PGA sheets	Absent	14
Late (2016)	71	Male	M	Lesser curvature	25	43	2	PGA sheets	Absent	13
Late (2018)	82	Female	L	Greater curvature	12	15	Unclear	PGA sheets	Absent	12
Late (2018)	78	Male	M	Posterior wall	8	13	10	OTSC	Absent	16
Late (2020)	45	Female	U	Lesser curvature	15	4.9	5	Clipping	Absent	11
Late (2021)	55	Female	U	Greater curvature	5	13	5	OTSC	Absent	6
Late (2022)	82	Female	L	Greater	12	13	2	OTSC	Present	13

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				curvature						
Late (2022)	80	Female	M	Anterior wall	16	20	3	OTSC	Absent	13

U: Upper third, M: Middle third, L: Lower third, PGA: Polyglycolic acid, OTSC: Over-the-scope clip.

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Table 4. Factors associated with surgical operation for delayed perforation

	Surgical operation n = 9	No surgical operation n = 19	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age, years	68 (64–82)	70 (63–81)	1.0 (0.93–1.1)	1	1.0 (0.93–1.1)	0.59
Sex				0.432		0.083
Male	4 (44)	12 (63)	0.48 (0.07–3.1)		0.04 (0.001–1.5)	
Female	5 (56)	7 (37)	ref		ref	
Comorbidity				1		0.751
Present	4 (44)	9 (47)	0.89 (0.13–5.7)		0.66 (0.05–8.4)	
Absent	5 (56)	10 (53)	ref		ref	

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Longitudinal location				0.461		0.192
Upper third	5 (56)	7 (37)	2.1 (0.32–14.6)		6.2 (0.40–97)	
Middle/Lower third	4 (44)	12 (63)	ref		ref	
Circumferential location				0.368		0.613
Lesser curvature	3 (33)	5 (26)	1.4 (0.16–10.3)		0.49 (0.03–7.7)	
Others	6 (67)	14 (74)	ref		ref	
Endoscopic size, mm	20 (12–30)	15 (11–28)	1.0 (0.95–1.1)	0.639	1.0 (0.93–1.1)	0.915
Period				0.042		0.043
Early (before implementing PGA/OTSC)	7 (78)	6 (32)	ref		ref	
Late (after implementing	2 (22)	13 (68)	0.14 (0.02–0.83)		0.04 (0.002–0.9)	

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PGA/OTSC)						

Data are presented as the median (interquartile range) or n (%). *OR: Odds ratio, CI: Confidence interval,PGA: Polyglycolic acid, OTSC: Over-the-scope clip.*

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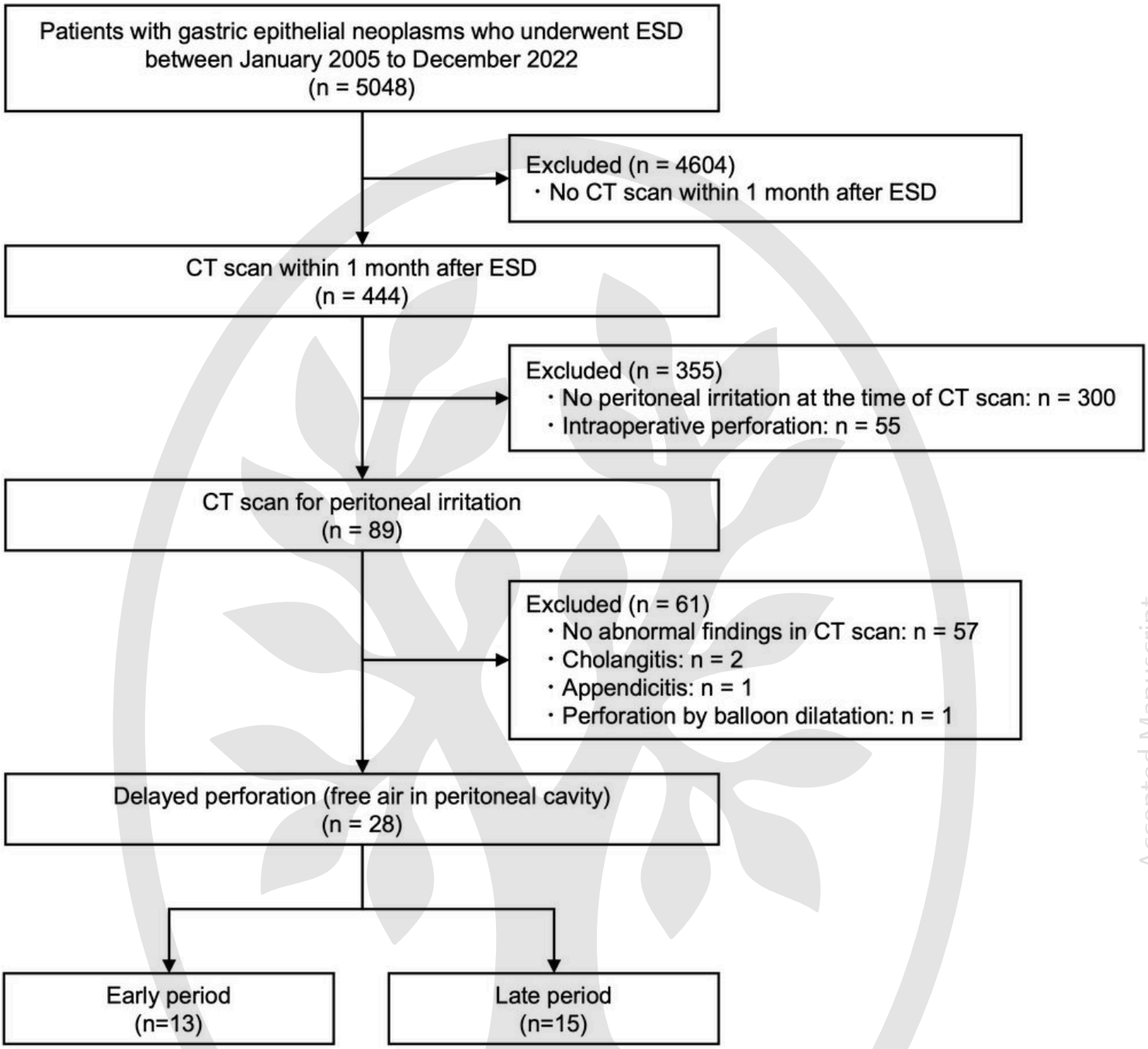

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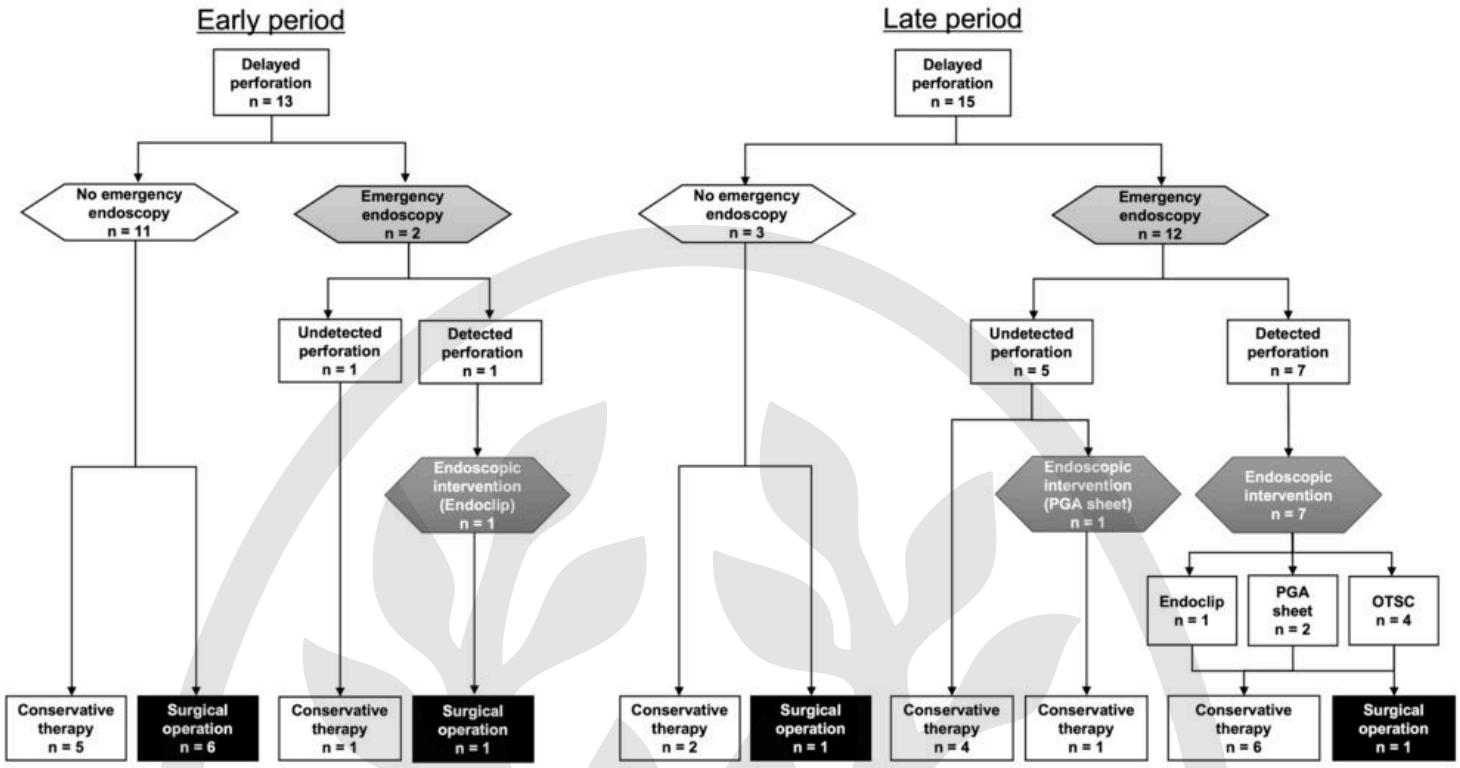

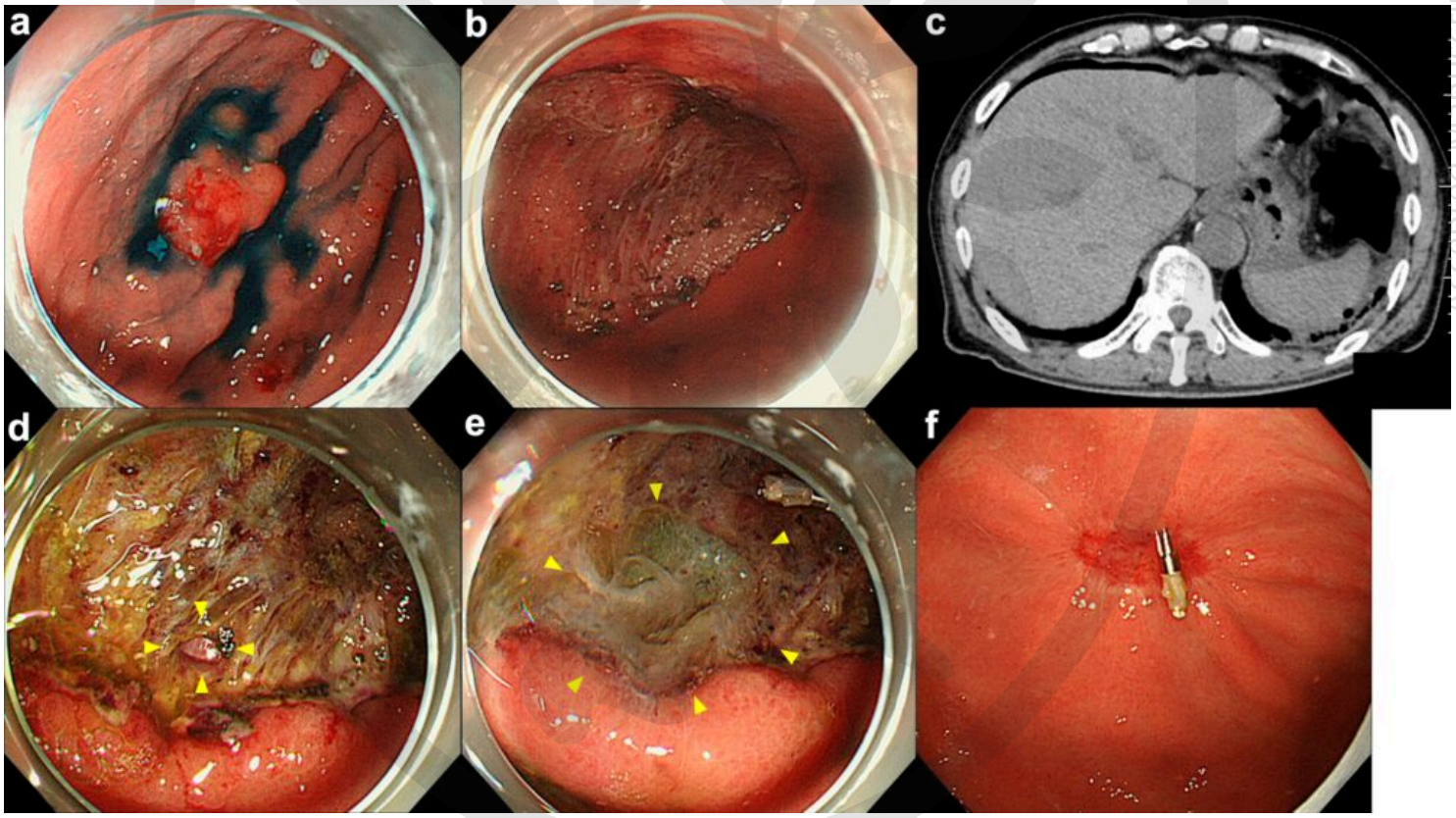

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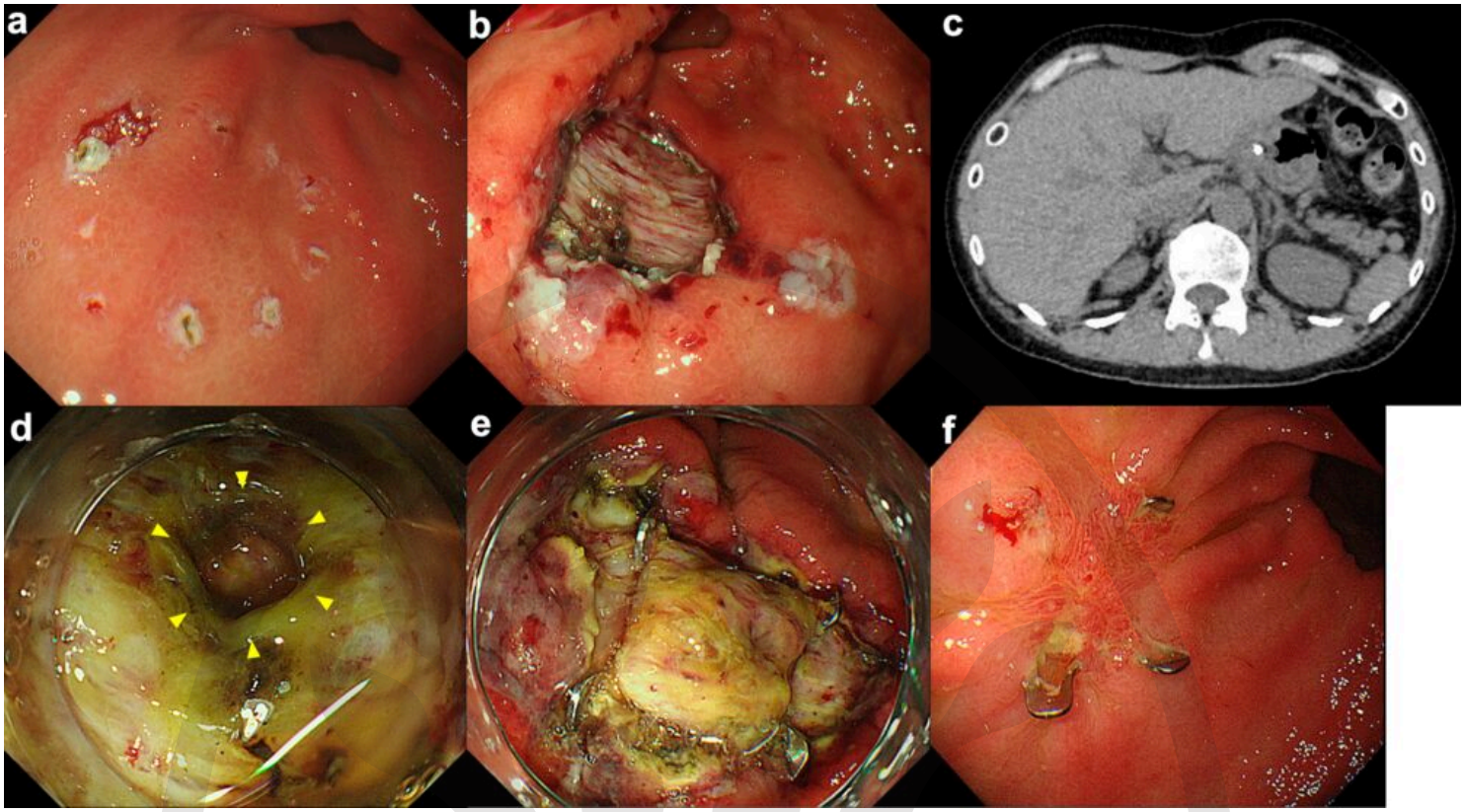

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