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Endoscopic submucosal dissection for early gastric cancer on the lesser curvature in upper third of the stomach is a risk factor for postoperative delayed gastric emptying

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Abstract

Background Advances in Endoscopic submucosal dissection (ESD) technology have established ESD for early gastric cancer as a safe and stable technique. However, ESD may induce delayed gastric emptying and the cause of food residue retention in the stomach after ESD is not clear. This study aimed to clarify risk factors for delayed gastric emptying with food retention after gastric ESD.

Methods We retrospectively examined for food residue in the stomach 1 week after ESD was performed for early gastric carcinoma at Osaka Saiseikai Nakatsu Hospital from February 2008 to November 2016.

Results Food residue was observed in 68 (6.1%) of 1114 patients who underwent gastric ESD. The percentage of lesions located on the lesser curvature of the upper third of the stomach was 45.6% (31/68) in the food residue group and 3.5% (37/1046) in the non-food residue group, which was significantly different ($P < 0.01$). Multivariate logistic regression analysis revealed that lesions on the lesser curvature of the upper third of the stomach (Odds ratio [OR] 23.31, 95% confidence interval [CI] 12.60–43.61, $P < 0.01$), post-ESD bleeding (OR 4.25, 95%CI 1.67–9.80, $P < 0.01$), submucosal invasion (OR 2.80, 95%CI 1.34–5.63, $P < 0.01$), and age over 80 years (OR 2.34, 95%CI 1.28–4.22, $P < 0.01$) were independent risk factors for food retention after gastric ESD. Of the 68 patients, 3 had food residue in the stomach on endoscopic examination for follow-up observation after the ESD ulcer had healed.

Conclusions Delayed gastric emptying with food retention after gastric ESD was associated with lesions located in the lesser curvature of the upper stomach, submucosal invasion of the lesion, age older than 80 years, and post-ESD bleeding, though it was temporary in most cases.

Keywords Endoscopic submucosal dissection · Gastric emptying · Food residue · Lesser curvature · Post-ESD bleeding · Submucosal invasion

Gastric cancer is the third common cause of cancer death in the world [1]. Improvement of diagnostic systems, such as magnifying endoscopy and narrow-band imaging, has made it possible to detect and treat gastric cancer at an earlier stage [2]. Endoscopic submucosal dissection (ESD) is a minimally invasive treatment for early gastric cancer (EGC) with high *en bloc* resection rates, low adverse events, and maintenance of postoperative gastric function [3]. However, clinical symptoms, such as fatigue, pain, and appetite loss, may develop after ESD and bother patients [4, 5]. Therefore, the safety and feasibility of ESD as well as the quality of life (QOL) after ESD are important.

Food residue in the stomach is rarely found during endoscopy because patients fast before examination. However, it is observed in 9.4–18.7% of the remaining stomach after distal gastrectomy [6–8]. This is due to delayed gastric emptying from gastrectomy, and food residue disturbs detection of metachronous cancer. Large-sized ESD in the pylorus may cause post-ESD stricture, which leads to a large amount of residual food in the stomach [9]. However, even ESD

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without post-ESD stricture can induce delayed gastric emptying [4, 10]. Delayed gastric emptying is reflected by the amount of remaining food, and food retention may be used as an indicator of clinical gastroparesis [11]. To the best of our knowledge, there is no study examining delayed gastric emptying with food retention after gastric ESD. This study aimed to clarify risk factors for delayed gastric emptying after gastric ESD.

Patients and methods

Between February 2008 and November 2016, 1235 patients with EGC were treated by ESD at Osaka Saiseikai Nakatsu Hospital. Among them, 55 patients with synchronous lesions, 25 patients with remnant stomach, 10 patients who had food residue during endoscopy before ESD, and 31 patients who did not undergo second-look endoscopy at 1 week after ESD were excluded from the present study (Fig. 1). Our indication criteria for gastric ESD were in accordance with the treatment guidelines for gastric cancer published by the Japanese Gastric Cancer Association (JGCA) [12]. The macroscopic EGC type was divided into two groups based on the criteria of JGCA as follows: elevated type, 0-I (+IIa), 0-IIa (+IIb, + IIc); flat/depressed type, 0-IIb, 0-IIc (+IIa, +III). The location of EGC was categorized as upper third, middle third, or lower third of the stomach. The procedure time was defined as the time between the first submucosal injection to lift the target lesion and completion of the dissection. *En bloc* resection was defined as single piece resection.

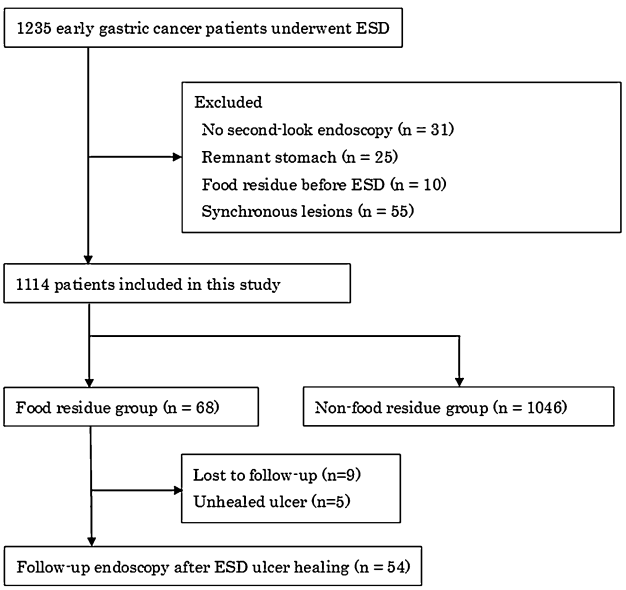

Fig. 1 Flowchart outlining the design of the study

R0 resection was histologically defined as tumor removal of a single piece with tumor-free lateral and vertical margins. The lesion size, depth of invasion, histological type, lymphatic invasion, venous invasion, and ulceration were assessed histopathologically. The differentiated type included well or moderately differentiated adenocarcinoma or papillary adenocarcinoma, and the undifferentiated type included poorly differentiated adenocarcinoma or signet-ring cell carcinoma. In the case of mixed histological types, type was determined by the dominant histological features. Experts were defined as having performed more than 50 ESD for EGC. We retrospectively reviewed all pictures of the second-look endoscopies at 1 week after ESD to examine food retention in the stomach. All patients were informed of the risks and benefits of ESD, and provided written informed consent. The study protocol was approved by the ethics committees of Osaka Saiseikai Nakatsu Hospital.

ESD procedures

All patients fasted from 21:00 on the day before ESD. ESD procedures were carried out under intravenous sedation with midazolam and pethidine hydrochloride. During the procedure, blood pressure, pulse rate, electrocardiograph, and oxygen saturation were monitored, and carbon dioxide insufflation was used through a channel endoscope. A single-channel endoscope with a water jet (GIF-Q260J; Olympus, Tokyo, Japan) was used with a transparent hood (F-030 or view opener; Top, Tokyo, Japan) mounted onto the tip of the endoscope. An ICC 200 or VIO 300D (ERBE Elektromedizin GmbH, Tübingen, Germany) was used as the electrosurgical generator. After dot marking outside the lesion delineated by chromoendoscopy, a saline solution with or without epinephrine was injected into the submucosal layer to lift the lesion. A circumferential incision was made around the lesion with a FlushKnife BT (Fujifilm Medical, Tokyo, Japan) or a needle knife and an insulated-tipped (IT) knife 2 (KD-611L; Olympus) outside the markings. The submucosal layer beneath the lesion was dissected using the same IT knife 2 or FlushKnife BT until complete removal. Large or bleeding vessels in the submucosa, and visible exposed vessels on the ulcer bed were coagulated using the Coagrasper (FD-410LR; Olympus). Bleeding related with the procedure was defined when one of the following conditions was observed requiring endoscopic hemostasis: decrease in total hemoglobin by more than 2 g/dl compared with the last preoperative level or massive melena after ESD without other apparent source of bleeding. Perforation was diagnosed endoscopically during the ESD procedure, or by the presence of free air on abdominal plain radiography or computed tomography image.

Presence of food residue

Patients were allowed to drink water on the day after ESD if there were no problems in terms of their general condition and blood test results. Light meal intake was allowed 2 days after ESD and regular diet was resumed 5 days after ESD. In the state of being hospitalized, second-look endoscopy was performed 1 week after ESD. All patients ate a regular meal of fixed quantity at 18:00 the day before endoscopy and fasted from 21:00 until the endoscopic examination. All patients underwent endoscopy between 9:00 and 13:00. They were discharged the next day after second-look endoscopy. The degree of food residue was classified with the following criteria: Grade 0; no food residue, Grade 1; a small amount of food residue, Grade 2; a moderate amount of food residue, and Grade 3; a large amount of food residue (Fig. 2) [7, 8, 13]. Presence of food residue (FR group) was defined as food residue of grade 2 or 3, and absence of food residue (non-FR group) was defined as food residue of grade 0 or 1.

Follow-up endoscopy after ESD

All patients took proton pump inhibitors from the day before ESD for 2 months. The first follow-up endoscopy was performed 3 months after ESD, and subsequent surveillance endoscopies were performed every 1 year. The presence of food residue after post-ESD ulcer healing was evaluated in the FR group (Fig. 3).

Statistical analysis

Categorical data were described by proportions, and differences between groups were assessed using Pearson's Chi-square or Fisher's exact test when appropriate. Continuous variables were the median when non-normally distributed. Continuous and non-normally distributed variables were compared using the Wilcoxon rank sum test. Risk factors for food retention after gastric ESD were analyzed by multivariate logistic regression analysis. All *P* values were two

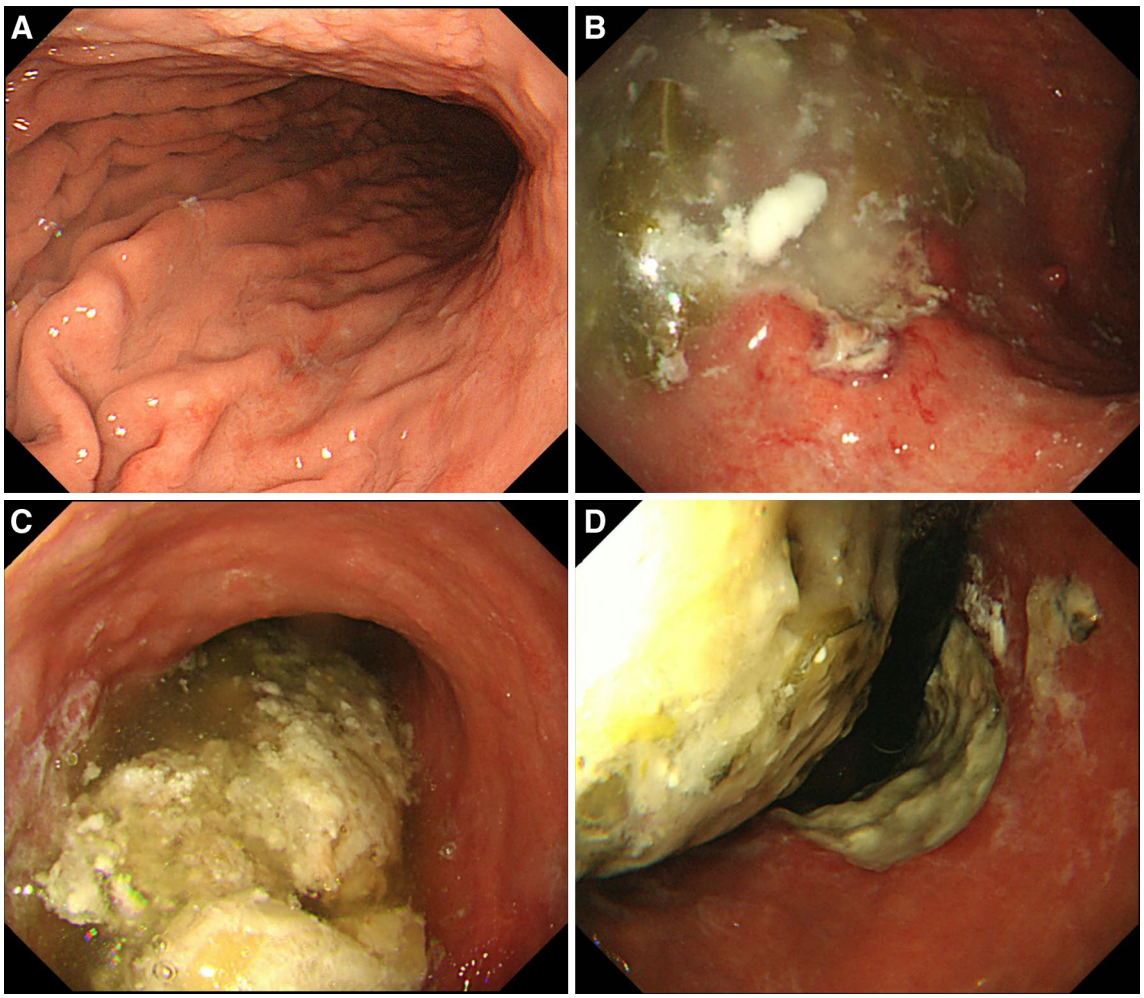

Fig. 2 Degree of food residue. **A** Grade 0; no food residue, **B** Grade 1; a small amount of food residue, **C** Grade 2; a moderate amount of food residue, **D** Grade 3; a large amount of food residue

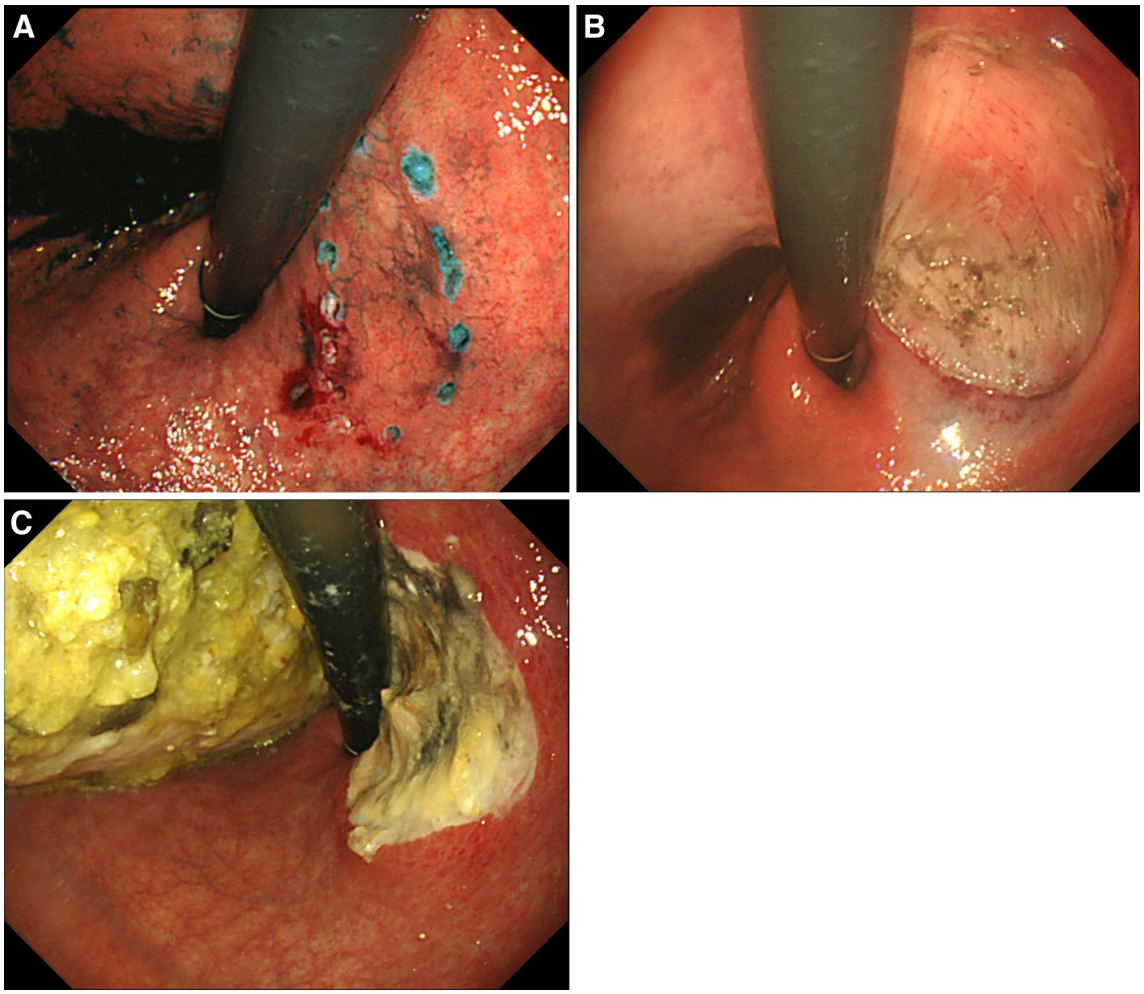

Fig. 3 Food residue after endoscopic submucosal dissection (ESD). **A** Before ESD, **B** Ulcer bed after ESD, **C** Food residue one week after ESD

sided, and P values of <0.05 were considered significant. All statistical analyses were performed using JMP version 11 (SAS Institute, Cary, North Carolina, USA).

Results

Characteristics of the patients and resected lesions

A total of 1114 patients were included in this study, and food residue was observed in 68 patients (6.1%). Characteristics of the patients and the lesions are summarized in Table 1. Patients in the FR group were older than those in the non-FR group (78 years, interquartile range [IQR] 71–81 years; 72 years, IQR 66–78, respectively, $P<0.01$). The median size of the lesions was 16 mm (IQR 10–27 mm) in the FR group and 12 mm (IQR 8–19 mm) in the non-FR group, which was significantly different ($P<0.01$). As for lesion location, the proportion of lesions in the upper third of the stomach was higher in the FR group than in the non-FR group (60.3 vs. 13.7%, $P<0.01$). Furthermore, the relationship between more detailed location of the lesions and food residue is shown in Fig. 4. The percentage of lesions located on the lesser curvature of the upper third of the stomach was 45.6% (31/68) in the FR group and 3.5% (37/1046) in the non-FR group, which was significantly different ($P<0.01$). There was no significant difference between the two groups in sex, macroscopic types, tumor differentiation, lymphatic invasion, venous invasion, ulceration, or atrophic types.

Clinical outcomes and adverse events

The clinical outcomes and adverse events of ESD are shown in Table 2. The median procedure time in the FR group was 55 min (IQR 30–121 min), which was significantly longer than that in the non-FR group (38 min, IQR 23–67 min, $P<0.01$). Post-ESD bleeding was more frequent in the FR group (13.2%) than in the non-FR group (4.7%, $P<0.01$). In

Table 1 Characteristics of the patients and resected lesions

	Presence of food residue	Absence of food residue	*P* value
Lesions	68	1046	
Age, median (IQR), years	78 (71–82)	72 (66–78)	< 0.01
Sex, n (%)			0.79
Male	46 (67.6)	728 (69.6)	
Female	22 (32.4)	318 (30.4)	
Macroscopic types, n (%)			0.31
Elevated	43 (63.2)	588 (56.2)	
Flat or depressed	25 (36.8)	458 (43.8)	
Lesion size, median (IQR), mm	16 (10–27)	12 (8–19)	< 0.01
Resected specimen size, median (IQR), mm	40 (31–50)	37.5 (30–46)	0.10
Lesion location, n (%)			< 0.01
Upper third	41 (60.3)	143 (13.7)	
Middle third	17 (25.0)	467 (44.6)	
Lower third	10 (14.7)	436 (41.7)	
Circumference, n (%)			0.02
Greater curvature	8 (11.8)	215 (20.6)	
Anterior wall	11 (16.2)	217 (20.7)	
Lesser curvature	38 (55.9)	390 (37.3)	
Posterior wall	11 (16.2)	224 (21.4)	
Depth of invasion, n (%)			< 0.01
M	51 (75.0)	941 (90.0)	
SM	17 (25.0)	105 (10.0)	
Differentiation of lesion, n (%)			0.16
Differentiated type	68 (100)	1009 (96.5)	
Undifferentiated type	0 (0)	37 (3.5)	
Lymphatic invasion, n (%)	5 (7.4)	45 (4.3)	0.22
Venous invasion, n (%)	0 (0)	6 (0.6)	1.00
Ulceration, n (%)	8 (11.8)	73 (7.0)	0.15
Open type atrophy, n (%)	66 (97.1)	980 (93.7)	0.43

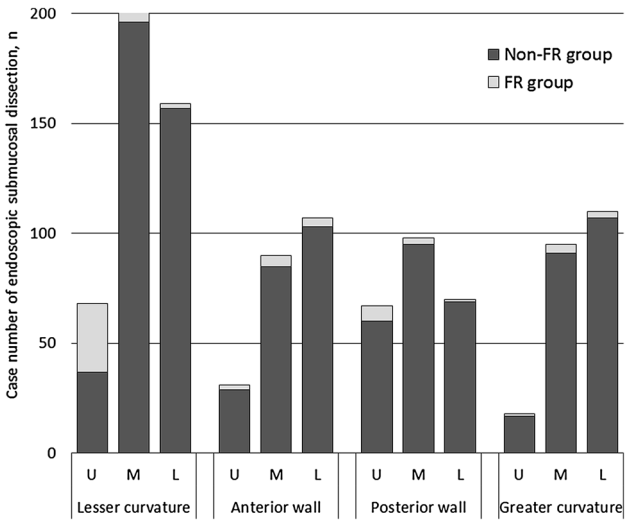

Fig. 4 Association of food residue and location of the lesions. *U* upper third of the stomach, *M* middle third of the stomach, *L* lower third of the stomach

addition, all postoperative bleeding in the FR group occurred more than 7 days after ESD. There was no significant difference between the two groups in *en bloc* resection rate (98.5 vs. 98.5%), R0 resection rate (88.2 vs. 92.4%), or perforation rate (8.8 vs. 4.4%).

Risk factors for delayed gastric emptying after gastric ESD

In the multivariate logistic regression analysis, lesions located in the lesser curvature of the upper third of the stomach (Odds ratio [OR] 23.31, 95% confidence interval [CI] 12.60–43.61, $P < 0.01$), post-ESD bleeding (OR 4.25, 95%CI 1.67–9.80, $P < 0.01$), submucosal invasion of the tumor (OR 2.80, 95%CI 1.34–5.63, $P < 0.01$), and age over 80 years (OR 2.34, 95%CI 1.28–4.22, $P < 0.01$) were independent risk factors for food retention after gastric ESD (Table 3). However, treatment time longer than 60 min and lesion size > 20 mm were not correlated with food retention

Table 2 Clinical outcomes and adverse events

	Presence of food residue	Absence of food residue	*P* value
Treatment time, median (IQR), min	55 (30–121)	38 (23–67)	< 0.01
Operators, n (%)			0.68
Experts	47 (69)	747 (71)	
Trainees	21 (31)	299 (29)	
En bloc resection, n (%)	67 (98.5)	1030 (98.5)	0.62
R0 resection, n (%)	60 (88.2)	966 (92.4)	0.24
Adverse events, n (%)			
Postoperative bleeding	9 (13.2)	49 (4.7)	< 0.01
Perforation	6 (8.8)	46 (4.4)	0.13

Table 3 Multivariate analysis of risk factors related with delayed gastric emptying after gastric ESD

	Odds ratio	*P* value	95% confidence interval
Lesser curvature of the upper third	23.31	< 0.01	12.60–43.61
Submucosal invasion	2.80	< 0.01	1.34–5.63
Age > 80 years old	2.34	< 0.01	1.28–4.22
Lesion size > 20 mm	0.97	0.93	0.50–1.83
Treatment time > 60 min	1.35	0.32	0.74–2.45
Postoperative bleeding	4.25	< 0.01	1.67–9.80

Table 4 Follow-up endoscopy after ESD ulcer healing

Follow-up rate, n (%)	54 (79.1)
Days after ESD (IQR), days	90 (70–108)
Presence of food residue, n (%)	3 (5.6)

(OR 1.35, 95%CI 0.74–2.45, $P = 0.32$; OR 0.97, 95%CI 0.50–1.83, $P = 0.93$, respectively).

Presence of food residue after ESD ulcer healing

In the FR group, follow-up endoscopies were performed for 54 patients (79.1%) after the ESD ulcer healed (Table 4). The post-ESD ulcer was not fully healed at the follow-up endoscopy in 5 patients and 9 patients were lost to follow-up. Food residue was observed in 3 patients (5.6%) during follow-up endoscopy.

Discussion

Major adverse events of gastric ESD are perforation, delayed bleeding, and aspiration pneumonia, which prevents successful endoscopic treatment. On the other hand, even if ESD finished successfully, delayed gastric emptying occurred at a frequency of 6.1% as a side effect of ESD in our study. Previous studies showed that premenopausal young women in healthy volunteer had a slower gastric emptying [14, 15]. Additionally, delayed gastric emptying occurs as a result of invasive treatment [4, 6–8, 10, 16–18]. Food residue was reported in 9.4–18.7% of the remaining stomachs observed following distal gastrectomy [6–8]. These studies found that food residue was reduced by fasting for over 18 h and controlling the diet on the day before endoscopic examination. Gastric dysmotility was reported to develop in patients who underwent laparoscopic and endoscopic cooperative surgery (LECS) [16], and ablation for atrial fibrillation [17, 18]. Moreover, delay of gastric emptying was found to develop 1 week after ESD in other studies [4, 10]. However, in one of these studies, food residue was not evaluated, and another was a small study with only four patients (7.4%) in whom food residue was observed after ESD.

In our study, lesions located in the lesser curvature of the upper third of the stomach, submucosal invasion of the tumor, age older than 80 years, and post-ESD bleeding were associated with food retention in the stomach after ESD. Watanabe et al. reported that delay of gastric emptying after gastric ESD occurs more frequently in proximal lesions than in distal ones because the muscle of proximal stomach is thinner than that of the distal stomach, and muscle injury by electrocauterization may affect the gastric emptying function [4]. However, gastric peristalsis is generated from a pacemaker region in the greater curvature of upper stomach and propagates toward the pylorus [19], and peristalsis is minimal in the lesser curvature of the upper stomach. Therefore, we speculated that ESD in the upper stomach affected the propagation of peristalsis rather than local peristalsis.

Waseda et al. reported that two of four patients with gastric submucosal tumors located in the lesser curvature of the gastric body who received LECS developed gastric dysmotility after the procedure, although none of the patients with tumors located in other areas of the stomach developed it [16]. In this study, resection of Latarjet's branch of the vagal nerve was assumed to negatively affect gastric motility. Ablation for atrial fibrillation may also cause gastroparesis, presumably by injury of the periesophageal vagal nerve [17, 18]. Similarly, gastroparesis after gastric ESD may have been due to injury of Latarjet's branch in our study. Fibrosis and granulation after gastric ESD have been observed not only in the submucosal layer but also in the muscularis propria layer [20]. Jiang et al. reported that in laparoscopy-assisted gastrectomy after ESD, preservation of the coeliac branch of the vagal nerve was difficult [21]. This suggests that inflammation and electrocauterization caused by ESD in the lesser curvature of upper stomach damages Latarjet's branch of the vagal nerve surrounding the stomach.

When gastric cancer invades over lamina muscularis mucosae, ESD must be performed in the deeper submucosal layer, and inflammation derived from ESD may affect more outside the stomach. In the previous report, changes in gastric emptying with age, especially in elderly people, are controversial [14, 22]. However, our findings indicate that older age is associated with delayed gastric emptying after ESD. Although the gastric ESD of the elderly has been reported to be acceptable [23, 24], we need to care about their gastric dysmotility after ESD. Delayed bleeding in patients with food residue was seen over 1 week after ESD, which implies that gastric dysmotility after ESD caused delayed bleeding. It is possible that the non-elastic artificial ulcer was stimulated by extension of the full stomach due to dysmotility, which led to bleeding.

Gastrointestinal obstruction may cause food residue in the stomach after ESD. Post-ESD stenosis occurred in 7% of patients who underwent pyloric resection and they had food residue in the stomach [9]. In this study, post-ESD stricture developed at 1 month after ESD due to healing of the ulcer. However, in the present study, food residue was observed 1 week after ESD when the artificial ulcer was hardly epithelialized. Although hyperphagia before endoscopic examination may be the cause of food residue in the stomach, all patients followed the hospital diet and did not overeat.

Delayed gastric emptying after ESD is very likely to be transient. In our study, only three patients (5.6%) of the FR group still had food residue after the post-ESD ulcer had healed and most cases did not have food residue. The fact that gastric dysmotility was temporary denies the possibility of permanent nerve destruction. On the other hand, temporary impact on nerve conduction can be a possible explanation. In this respect, it is contrast to patients who had gastrectomy suffering from food residues for long term [6–8]. However, temporary gastroparesis may lower QOL of the patients after ESD. Kim at el. reported that fatigue, pain, and appetite loss increased 7 days after ESD, although these symptoms eventually improved [5]. Additionally, Watanabe et al. demonstrated that 16.7% of patients who underwent gastric ESD had clinical symptoms 1 week after ESD; however, only 1.9% of them had these symptoms 2 months later [4]. This course corresponds with the period of food residue retention in our study.

This study has several limitations. First, it was a retrospective analysis at a single institution. Second, patients' comorbidity and physical condition have not been evaluated. Diabetes and Parkinson's disease are reported as risk factors of delayed gastric emptying [25, 26]. Moreover, it is theoretically possible that the patients with proximal gastric lesions had a higher incidence of delayed gastric emptying. Our findings may reflect not only the effect of ESD but also one of these diseases. However, we believe that the effects for gastric dysmotility by any other factors than ESD were reduced because patients who had food residue at preoperative endoscopy were excluded from this study. Third, gastric emptying was not evaluated in detail. Though scintigraphy and a breath test with ^{13}C-labeled acetic acid are often used to evaluate gastric emptying [4, 10, 11, 14, 15, 17, 22], we evaluated only with food residues in the stomach. Coleski at el. reported that the degree of food residue in the stomach was associated with gastric emptying [11]. In this study, only 26% of patients with delayed gastric emptying had food residue 4 h after a meal. Another study reported that only 0.3% of patients without a history of gastrectomy had food residue over 12 h after a meal [6]. Therefore, food residue retention over 12 h after a meal in our study may clinically suggest the presence of post-ESD delayed gastric emptying. However, in order to make a more accurate and objective evaluation of gastric emptying function, it is desirable to conduct a prospective study using modalities such as scintigraphy and carbon breath test before and after ESD. Fourth, we couldn't collect enough detailed data in regard to patients' symptom for delayed gastric emptying. Assessment of the relationship between food retention and symptoms after ESD would also be warranted in the future study.

In conclusion, delayed gastric emptying after gastric ESD was associated with lesions located in the lesser curvature of the upper stomach, submucosal invasion of the tumor, age older than 80 years, and post-ESD bleeding, though it was temporary in most cases. Further studies should be conducted to evaluate the relationship between food retention and symptoms after ESD and correlate these data with more objective measure such as scintigraphy studies.

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Compliance with ethical standards

Disclosures Tetsuya Yoshizaki, Daisuke Obata, Yasuhiro Aoki, Norihiro Okamoto, Hiroki Hashimura, Chise Kano, Megumi Matsushita, Atsushi Kanamori, Kei Matsumoto, Masahiro Tsujimae, Kenji Momose, Takaaki Eguchi, Shunsuke Okuyama, Hiroshi Yamashita, Mikio Fujita, Akihiko Okada have no conflicts of interest or financial ties to disclose.

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