Timing of pyloric stenosis and effectiveness of endoscopic balloon dilation after pyloric endoscopic submucosal dissection

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Running head

Timing of pyloric stenosis

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Disclosure statement

Takashi Toyonaga has received a portion of the sales of Flush knife-BT and Flush Knife-BTS, which were developed in collaboration with FUJIFILM Medical Co, as royalties. He has also received a portion of the sales of Coagrasper G, which were developed in

collaboration with Olympus Corporation, as royalties. The other authors have no conflicts of interest or financial ties to disclose.

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ABSTRACT

Background and Aim: There have been studies on risk factors for stenosis after pyloric endoscopic submucosal dissection (ESD). However, the most appropriate strategies for the management of cases with these risk factors have not been established. This study aimed to investigate post-ESD management by evaluating the timing of stenosis and the effectiveness of endoscopic balloon dilation (EBD) after pyloric ESD. **Methods:** We retrospectively reviewed cases of pyloric ESD. We first reassessed risk factors for stenosis in multivariate analysis and receiver operating characteristic curve, and defined patients with the identified risk factors as the risk group. The primary outcome was the timing of stenosis in the risk group assessed by the Kaplan-Meier method. **Results:** We reviewed 159 cases with pyloric ESD and observed pyloric stenosis in 25 cases. Cases with circumferential mucosal defect ≥76% were identified as the risk group. The stenosis-free probability in the risk group was 97% (95% CI: 79–100%), 94% (95％ CI: 76–98%), and 85% (95% CI: 66–93%) on days 7, 14, and 21, respectively. It decreased every week thereafter and did not significantly change after day 56. Twenty-three stenosis cases, except for conservative improvement, including six whole circumferential pyloric ESD cases, were improved by EBD without complications. **Conclusions:** Post-ESD stenosis often developed from the 3rd to the 8th week. In all pyloric ESD cases, including whole circumferential pyloric ESD cases, pyloric stenosis was improved following EBD without complications.

Key Word

pyloric stenosis, pyloric endoscopic submucosal dissention, endoscopic balloon dilation, perforation, pyloric ESD, EBD

INTRODUCTION

Endoscopic submucosal dissection (ESD) is a treatment for early cancer without lymph node metastasis. It is known that ESD has early stage complications such as perforation and bleeding [1-3], however post-ESD stenosis is also a challenge as a late stage complication [4-9]. In general, post-ESD stenosis due to the large circumferential extent of mucosal defect with ESD in the esophagus is well known, and its occurrence rate is reported to be 7.1–18% [4-6]. It has been reported that the post-ESD stenosis rate in gastric ESD is 1.6–2.5% [7-9], which is lower than that of the esophagus, although the post-ESD stenosis rate in pyloric ESD is as high as 3.1–7.1% [10-12].

There have been several studies on stenosis in pyloric ESD, and it was reported that the circumferential extent of the mucosal defect greater than 3/4 and longitudinal mucosal defect greater than 5 cm were risk factors for pyloric stenosis [11, 12]. Endoscopic balloon dilation (EBD) was performed in cases with stenosis.

However, the management of patients with risk factors for stenosis has not been fully investigated. Because we did not know the actual timing of stenosis occurrence, we decided the timing of endoscopic follow-up and EBD based on the patient's vague symptoms and the discretion of the endoscopist. As a result, we were sometimes unable to detect the stenosis at an early stage, which led to poor patient condition such as vomiting [8, 13]. It was also unclear whether cases with whole circumferential pyloric ESD could be controlled by the same management method employed for patients with the risk factors of stenosis. For safe post-ESD management, it is important to know the timing of stenosis after pyloric ESD and to clarify the therapeutic effect of EBD including whole circumferential pyloric ESD for patients with stenosis risk factors.

Therefore, this study aimed to evaluate the timing of stenosis and the effectiveness of EBD after pyloric ESD, including whole circumferential pyloric ESD.

METHODS

Study design

This study was a retrospective observational study, and data were collected from electronic medical records at Kobe University Hospital and Kishiwada Tokushukai Hospital. The study protocol was approved by the Institutional Review Board of Kobe University Hospital (September 18, 2020). Informed consent was obtained by the opt-out method on the website.

Eligibility criteria for participants

We investigated 3,833 patients with 4,553 gastric epithelial neoplasms who underwent ESD at Kobe University Hospital and Kishiwada Tokushukai Hospital from January 2003 to March 2020. The study included 193 patients with 193 lesions who underwent pyloric ESD. Pyloric ESD was defined as any mucosal defect created by ESD in the pylorus ring. We excluded seven patients with seven lesions in whom gastrectomy was performed due to non-curative resection and 27 patients with 27 lesions in whom the postoperative course could not be followed-up at our hospital. Finally, we enrolled 159 patients with 159 lesions for this study (**Figure. 1)**.

ESD procedure

Endo-knives, such as the Flush knife, Flush knife-BT, Flush Knife-BTS, and IT knife (DK2618JN, DK2618JB, DK2620JBS; FUJIFILM Medical Co., Ltd., and KD-610L; Olympus Corporation, Tokyo, Japan), were used for mucosal and submucosal dissection. The ICC 200, VIO 300D, and VIO3 (Erbe Elektromedizin GmbH, Tübingen, Germany) were used as electrosurgical generators. We performed the submucosal dissection with endo-knives after local injection of saline with an injection needle. Hemostasis and vessel coagulation were

performed using endo-knives or hemostatic forceps (Coagrasper, Coagrasper G; Olympus Corporation, Tokyo, Japan) [14-18]. Locoregional triamcinolone injections were administered at the ulcer floor after ESD in some cases with wide circumferential mucosal defect. All patients received intravenous omeprazole (40 mg) for 2 days followed by oral rabeprazole or esomeprazole or vonoprazan (20 mg) daily for 2 months after ESD.

Definition of pyloric stenosis

Pyloric stenosis was defined as a condition in which an endoscope (GIF-Q230 or GIF-Q240 or GIF-Q260J or GIF-H260 or GIF-H290; Olympus Corporation, Tokyo, Japan) with a diameter of 10.5–11.9 mm could not pass through the pylorus, and improvement of stenosis was defined as the widening of the pylorus in response to EBD such that the endoscope can pass.

Post-ESD follow-up

The curability of the resected specimen was pathologically assessed using the standards of the Japanese gastric cancer treatment guidelines [19-21]. In general, we performed an additional gastrectomy with lymph node dissection when the resected specimen was pathologically diagnosed as a non-curative resection with a risk of lymph node metastasis. On the other hand, we performed EGD on the schedule below when the resected specimen was pathologically diagnosed as a curative resection with a little risk of lymph node metastasis. We typically performed EGD 2–3 months after ESD to confirm the healing of the ulcer and then every 6 or 12 months to check for recurrence. However, we performed EGD before the scheduled examination for patients with symptoms, such as fullness, abdominal pain, nausea, and vomiting, and for patients predicted by an individual endoscopist to have a high probability of post-ESD stenosis due to wide circumferential mucosal defect. For cases

judged to be at high risk of stenosis, follow-up EGD was performed at least one week after ESD, and then once every 1-2 weeks thereafter. If it was determined that there was no tendency for stenosis, the interval was extended gradually to one month.

EBD procedure

We performed EBD in cases with pyloric stenosis, except for conservative improvement during the follow-up period. We used a controlled radial expansion balloon dilator (CRE Wireguided Balloon Dilators; Boston Scientific Japan Corp., Tokyo, Japan) with a diameter of 12–15 mm, 15–18 mm, or 18–20 mm for EBD. We determined the balloon size according to the degree of stenosis and started EBD at a pressure of 0.5 standard atmosphere (atm). We increased the pressure by 0.5 atm to the point of resistance and maintained that pressure for one minute. We confirmed that there was no bleeding or perforation after dilation and repeated the same procedure until the scope passed through the pylorus. EBD was continued approximately once every 1-2 weeks until stenosis improved.

Outcomes

We first reassessed risk factors for post-ESD stenosis. The survey items for the risk factors for post-ESD stenosis were age, sex, macroscopic type of lesions, direct involvement of lesions into the pyloric ring, depth of invasion, ulcer findings, location of mucosal defect, circumferential extent of mucosal defect, and specimen diameter. The macroscopic type of lesions, location of mucosal defect and direct involvement of lesions into the pyloric ring were assessed endoscopically. Depth of invasion, ulcer findings, and specimen diameter were assessed pathologically. The circumferential extent of mucosal defects was measured using computer software (Windows Ink; Microsoft Corporation, Washington, the United States of America) **(Figure. 2)**. The circumferential extent of the mucosal defect was defined as the

ratio of the circumferential degree of the resected pyloric ring divided by the whole circumferential degree of the pyloric ring. The risk factors for stenosis were identified by performing univariate analysis followed by multivariate logistic analysis. Those with a risk factor greater than or equal to the cut-off value obtained by the receiver operating characteristic (ROC) curve was defined as the risk group when the factor was a continuous variable.

The primary outcome was the timing of stenosis after pyloric ESD in the risk group. Timing of stenosis was defined as the duration between ESD and stenosis confirmation.

The secondary outcomes were the stenosis improvement rate by EBD, perforation and bleeding rate by EBD, number of EBDs, duration of EBD, and maximum diameter of EBD. Furthermore, we evaluated the difference in the stenosis rate, stenosis improvement rate by EBD, number of EBDs, and duration of EBD between cases with whole circumferential pyloric resection and cases with non-whole circumferential pyloric resection in the stenosis risk group. Stenosis improvement rate was defined as the ratio of stenosis improvement cases with EBD divided by all EBD cases. Post-EBD perforation was diagnosed as free air in the abdominal cavity by roentgenography or abdominal computed tomography after the procedure. Perforation rate by EBD was defined as the ratio of cases with post-EBD perforation divided by all EBD cases. Post-EBD bleeding was defined as a condition requiring endoscopic hemostasis. Bleeding rate by EBD was defined as the ratio of cases with post-EBD bleeding divided by all EBD cases. Number of EBDs was defined as the number of dilations required to improve stenosis. Duration of EBD was defined as the period from the date of the first EBD to the date of the final EBD. Maximum diameter of the EBD was the maximum balloon expansion diameter during the entire EBD period.

Statistical analysis

Stenosis risk factors were first analyzed by using the Fisher's exact test and Mann-

Whitney U-test. The factors reported in previous studies and the significant factors in univariate analysis were used for multivariate logistic regression analysis. The optimal cut-off value that indicates optimum sensitivity and specificity for the circumferential extent of the mucosal defect was determined by the ROC curve. The Kaplan-Meier method was used to assess the cumulative incidence of stenosis. The log-rank test was used to assess the relationship between the interval from ESD to stenosis in the risk and non-risk groups. Characteristics in cases that underwent whole and non-whole circumferential pyloric ESD were analyzed using the Fisher's exact test and the Mann-Whitney U-test. Statistical significance was set at $p < 0.05$. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphic user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics of patients and risk factors of pyloric stenosis

Pyloric stenosis after pyloric ESD was observed in 16% (25/159) of the patients. The stenosis cases had a significantly higher number of cases with direct pyloric ring involvement than the non-stenosis cases (84% vs. 43%; $p<0.001$). Moreover, the stenosis cases had a significantly greater circumferential extent of the mucosal defect ($p<0.001$). The stenosis cases also had a significantly greater diameter of specimen than the non-stenosis cases ($p<0.001$) **(Table1)**. In the multivariate analysis, only a wider circumferential mucosal defect was extracted as a risk factor for stenosis (Odds ratio = 1.10; 95% confidence interval [95% CI] =1.06–1.15; $p<0.001$) **(Table2)**. The cut-off value for the circumferential extent of the mucosal defect that affected pyloric stenosis was 76% in the ROC curve (sensitivity=0.93, specificity=0.84, area under the curve=0.91). Therefore, the risk group included cases with the circumferential extent of the mucosal defect greater than or equal to 76% (n=31), and the

non-risk group included cases with circumferential extent of mucosal defect less than 76% (n=128). Locoregional triamcinolone injections were required for nine patients (all in the risk group).

Timing of pyloric stenosis

The cumulative stenosis-free probability and period for the cases after pyloric ESD is shown by the Kaplan-Meier method in **Figure. 3**. Median follow-up was 731 (interquartile range [IQR], 98-1877) days. The risk group had a significantly lower stenosis-free probability than the non-risk group ($p<0.001$). The stenosis-free probability in the risk group was 97% (95% CI: 79–100%) on day 7, 94% (95% CI: 76–98%) on day 14 and decreased to 84% (95% CI: 66–93%) on day 21. After, it gradually decreased every week, although it did not significantly change after the 56th day.

EBD for pyloric stenosis

There were 25 cases of pyloric stenosis, two of which improved conservatively. The characteristics of the 23 cases that underwent EBD are shown in **Table 3**. All cases that underwent EBD improved stenosis without complications, such as perforation and bleeding. The median number and duration of EBDs was 4 times (IQR, 2–6) and 21 days (IQR, 14–44), respectively. The median maximum diameter of EBD was 18 (IQR, 15–18).

Comparison of whole and non-whole circumferential pyloric ESD in the risk group

In the risk group, there were seven cases with whole circumferential pyloric ESD and 24 cases with non-whole circumferential pyloric ESD. The characteristics of whole (circumference=100%) and non-whole circumferential cases (76%≤ circumference <100%) in the risk group are shown in **Table 4**. No significant differences were observed in the

stenosis rate, number of EBDs, duration of EBD, and maximum diameter of EBD.

DISCUSSION

In this study, we evaluated the timing of stenosis after pyloric ESD and the effectiveness of EBD on stenosis, including cases of whole circumferential pyloric resection. As a result, in wide circumferential cases, it was found that the post-ESD stenosis often developed from the 3rd to the 8th week. In all cases of stenosis, including cases with whole circumferential pyloric resection, the stenosis was improved by EBD without perforation. It was also found that whole circumferential cases had a significantly higher stenosis rate than non-whole circumferential cases, although no significant differences were found in the stenosis improvement rate and methods of EBD.

Previous studies have reported only up to nine cases of stenosis after pyloric ESD [11,12]; therefore, the timing of stenosis and the effectiveness of EBD could not be fully evaluated. In addition, there have been no comprehensive studies of cases with stenosis after whole circumferential pyloric ESD; therefore, its characteristics and treatment methods have not been fully investigated. In this study, we were able to evaluate 25 cases of stenosis after pyloric ESD. Moreover, there were seven cases with whole circumferential pyloric ESD. Therefore, we were able to examine the timing of stenosis and the effectiveness of EBD after pyloric ESD as well as the characteristics of cases with whole circumferential pyloric ESD. In addition, previous studies did not describe how to measure the circumferential extent of mucosal defect, the diameter of longitudinal mucosal defects and their cutoff values. We accurately evaluated the circumferential extent of mucosal defects using a computer software and those of longitudinal mucosal defects by measuring the diameter of the resected specimens. Then, we used the ROC curve to determine the cutoff value of the circumferential extent of mucosal defect, which was a significant risk factor in multivariate analysis.

We considered possible explanations and implications from the results of this study. It was reported that the circumferential extent of the mucosal defect greater than or equal to 75% and longitudinal mucosal defect greater than 5 cm were risk factors for pyloric stenosis [11,12]; however, only the circumferential extent of the mucosal defect greater than or equal to 76% was the risk factor by multivariate analysis in this study. There was almost no stenosis in the non-risk group, although it was found that the pyloric stenosis in the risk group often developed from the 3rd to the 8th week. Therefore, endoscopic follow-up for stenosis was required in the risk group earlier than the follow-up for typical ulcers. This was especially important during the 3rd to the 8th week.

Additionally, it was found that the stenosis after pyloric ESD could be improved without perforation by EBD in all cases. In this study, the stenosis rate after pyloric ESD was 16% (25/159), which was higher than stenosis rate of the entire gastric ESD that was reported to be 1.6–2.5% [7-9]. Nevertheless, the perforation rate of EBD was 0% in this study, similar to previous studies of pyloric ESD [11,12], which was lower than perforation rate in the entire gastric EBD that was reported to be 7.8–8.3% [9,22]. This suggests that the EBD-induced perforation may be less likely to occur in cases with pyloric ESD. There was perforation due to EBD in the antral ESD without pyloric resection, although no perforation was observed in the cases with pyloric resection in previous reports [9,13]. This means that we need to consider antral ESD and pyloric ESD separately in the lower stomach ESD, which may be anatomically explainable. It is easy to obtain the dilating effect of EBD owing to the narrow lumen of the pylorus. However, perforation is unlikely to occur because of the pyloric sphincter, which is a strong ring of smooth muscle at the pylorus. Therefore, we recommend performing EBD for all cases of stenosis after pyloric ESD and continue regular EBD depending on the condition until the stenosis improves.

It was unclear whether cases with whole circumferential pyloric ESD could be

managed using the same methods used for cases with stenosis risk factors. In a study of 26 cases of esophageal ESD with whole circumferential resection, stenosis was observed in 62%, and 19% of them could not be improved by EBD [23]. In this study, there were no significant differences in stenosis rate and EBD methods between cases that underwent whole and non-whole circumferential pyloric ESD in the risk group. EBD improved in all six cases with stenosis after whole circumferential pyloric ESD without perforation. Therefore, it was found that whole circumferential pyloric ESD might also be possible without fear of unmanageable stenosis.

Our study had several limitations. First, it was a retrospective study based on medical records; therefore, it could be affected by selection and measurement bias. The timing of endoscopic follow-up and EBD intervals varied between cases. The selection criteria for cases using steroids were unclear. In fact, we administered locoregional triamcinolone injections only for patients with stenosis risk factors, and it was difficult to evaluate the usefulness of steroids in preventing stenosis. Second, it was conducted at two institutions; therefore, the results could be difficult to generalize. Nevertheless, we included all cases of pyloric ESD in our institutions, and pyloric stenosis was clearly defined by objective indicators. In addition, stenosis after pyloric ESD is rare, and it is difficult to collect the number of cases. Because this is the first study to evaluate as many as 25 cases of stenosis after pyloric ESD, it is considered to be a study with sufficient clinical significance.

In conclusion, we retrospectively studied the timing of stenosis and the effectiveness of EBD after pyloric ESD, including cases with whole circumferential pyloric ESD. Post-ESD stenosis after pyloric ESD often developed from the 3rd to the 8th week. In all cases of stenosis after pyloric ESD, the stenosis was improved by EBD without perforation.

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Tables

Table 1 Baseline characteristics of patients and risk factors for pyloric stenosis

	Total n=159	Stenosis (+) n=25	Stenosis (-) n=134	Univariate p-value
Age (years)	72 (65–78)	74 (68–83)	72 (65–78)	0.21
Gender				0.85
Female	39 (25%)	7 (28%)	32 (24%)	
Male	120 (76%)	18 (72%)	102 (76%)	
Direct pyloric ring involvement				<0.001
Present	78 (49%)	21 (84%)	57 (43%)	
Absent	81 (51％)	4 (16%)	77 (57%)	
Mucosal defect location				0.30
Lesser curve	69 (43%)	13 (52%)	56 (42%)	
Anterior wall	38 (24%)	3 (12%)	35 (26%)	
Greater curve	20 (13%)	2 (8.0%)	18 (13%)	
Posterior wall	32 (20%)	7 (28%)	25 (19%)	
Macroscopic type				0.37
Elevated	91 (57%)	17 (68%)	74 (55%)	
Depressed	63 (40%)	8 (32%)	55 (41%)	
Flat	5 (3.1%)	0 (0%)	5 (3.7%)	
Invasion depth				0.14
Mucosal	151 (95%)	22 (88%)	130 (97%)	
Submucosal	8 (5.0%)	3 (12%)	4 (3.0%)	
Ulcer finding				0.32

Absent	140 (88%)	20 (80%)	121 (90%)	
Present	19 (12%)	5 (20%)	13 (9.7%)	
Circumferential extent of mucosal defect (%)	55 (40–70)	84 (76–99)	53 (37–64)	<0.001
Specimen diameter (mm)	40 (33–50)	53 (44–65)	39 (32–45)	<0.001

Data represent the number of patients (%) or median (interquartile range)

Table 2 Risk factors for pyloric stenosis in multivariate logistic regression analysis

	Odd ratio (95% CI)	p-value
Direct pyloric ring involvement	1.10 (1.06–1.15)	0.81
Circumferential extent of mucosal defect (%)	1.19 (0.28–4.98)	<0.001
Specimen diameter (mm)	1.02 (0.98–1.05)	0.38

95% CI = 95% confidence interval

Table 3 Characteristics of the 23 cases that performed EBD

Improvement of stenosis	23 (100%)
Number of EBD (number)	4 (2–6)
Duration of EBD (day)	21 (14–44)
Maximum diameter of EBD (mm)	18 (15–18)
Complications	0 (0%)
Perforation	0 (0%)
Bleeding	0 (0%)

Data represent the number of patients (%) or median (interquartile range)

EBD = endoscopic balloon dilation

Table 4 Characteristics of whole and non-whole circumferential cases in the risk group

	Whole (circumference = 100%) n=7	Non-whole (76%≤ circumference <100%) n=24	p-value
Stenosis	6 (86%)	15 (63%)	0.37
Number of EBD	6 (5–6)	3 (2–5)	0.15
Duration of EBD (day)	40 (37–43)	16 (14–50)	0.69
Maximum diameter of EBD (mm)	17 (16–18)	17 (15–18)	0.86

Data represent the number of patients (%) or median (interquartile range)

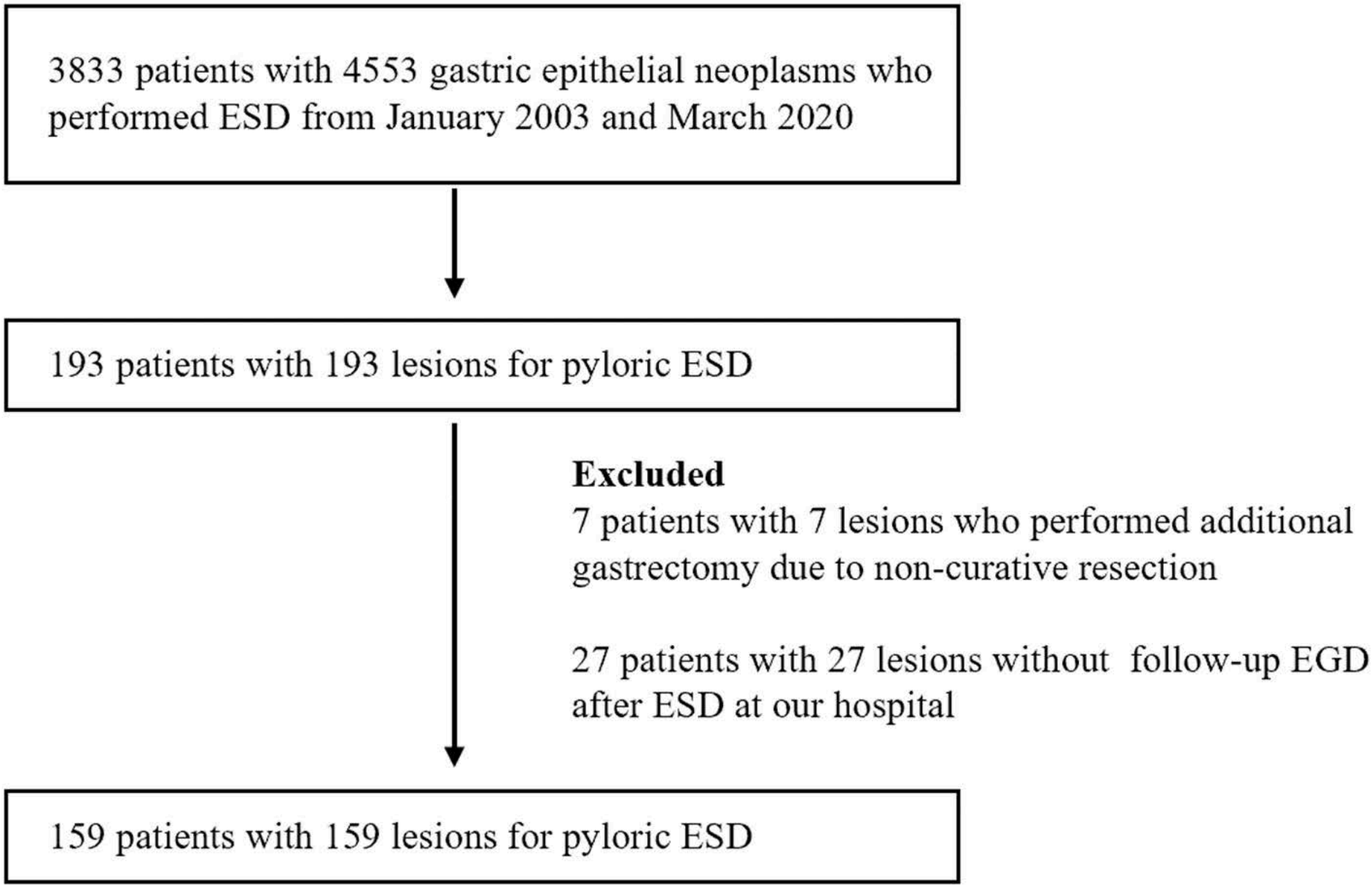
EBD = endoscopic balloon dilation

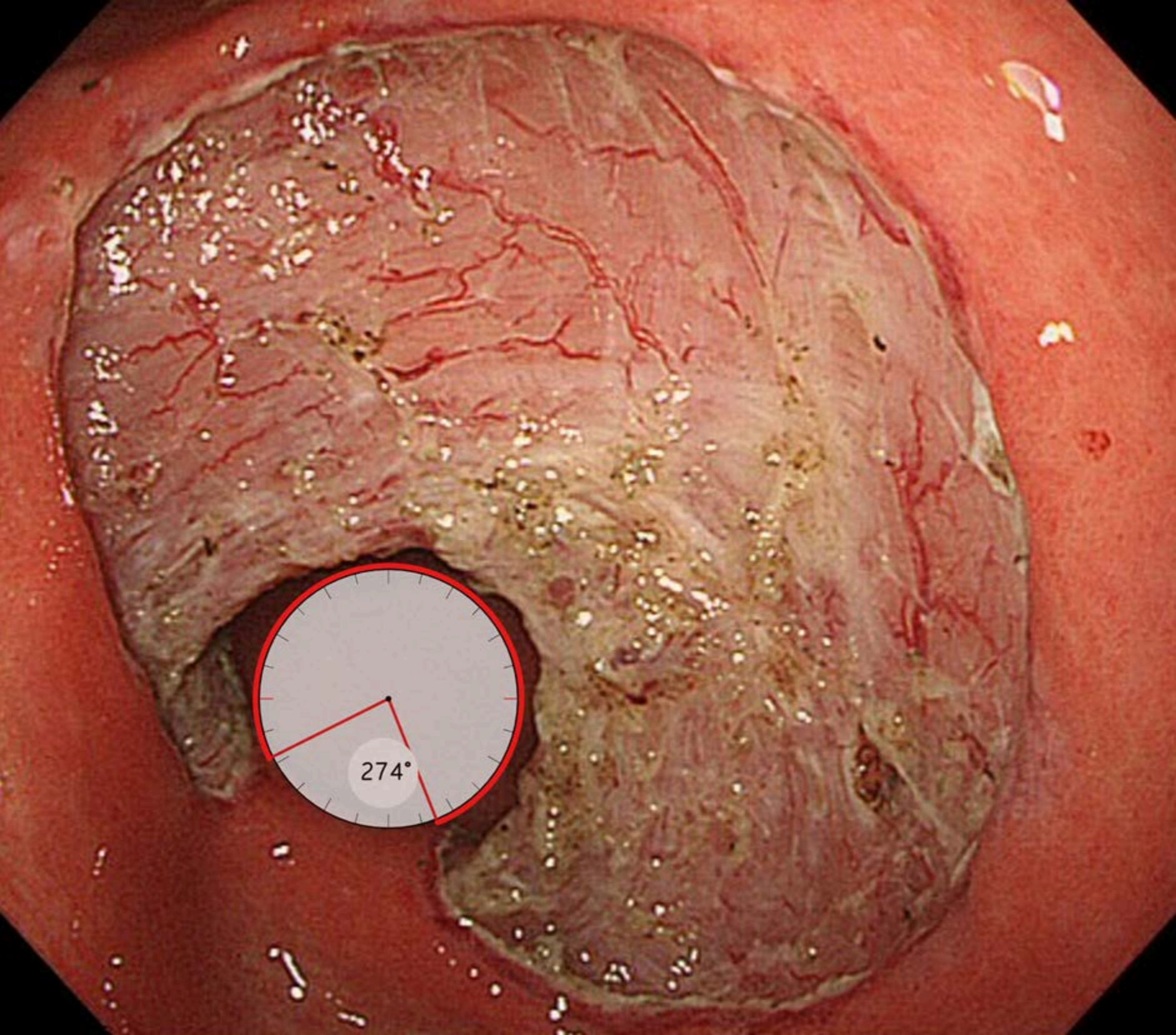
Figure legends

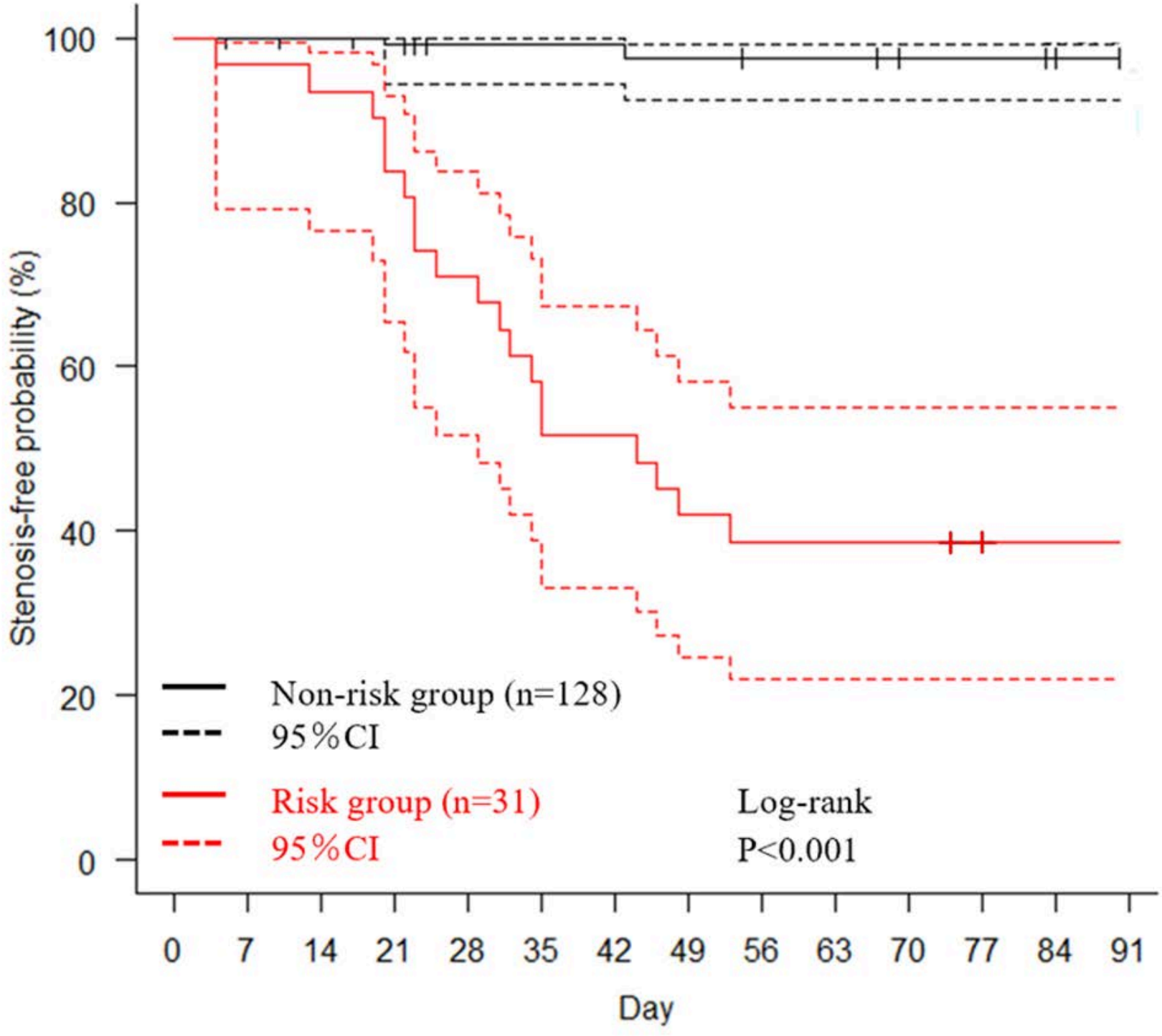
Figure. 1 The flow chart of patients and lesions included in this study. Finally, we selected 159 patients with 159 lesions as the subjects of this study.

Figure. 2 The circumferential extent of mucosal defect is calculated using a computer software. In this figure, the circumferential rate of mucosal defect is 76% because 274° is divided by 360°.

Figure. 3 The cumulative stenosis-free probability and period for the cases after pyloric endoscopic submucosal dissection (ESD) is shown by the Kaplan-Meier method. The Risk group is indicated by the red line and The Non-risk group is indicated by the black. The 95% confidence interval (95% CI) is shown by the dotted line.


3833 patients with 4553 gastric epithelial neoplasms who performed ESD from January 2003 and March 2020
193 patients with 193 lesions for pyloric ESD
Excluded
7 patients with 7 lesions who performed additional gastrectomy due to non-curative resection
27 patients with 27 lesions without follow-up EGD after ESD at our hospital
159 patients with 159 lesions for pyloric ESD


274°



Stenosis-free provability (%)														
Non-risk group	100	100	100	99	99	99	99	98	98	98	98	98	98	98
Risk group	100	97	94	84	71	52	52	42	39	39	39	39	39	39