Digestive and Liver Disease 51 (2019) 675–680

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Digestive Endoscopy

Clinical outcomes of endoscopic treatment for gastric epithelial neoplasm in remnant stomach after distal gastrectomy

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ARTICLE INFO

Article history:
Received 26 April 2018
Accepted 30 November 2018
Available online 17 January 2019

Keywords:
Argon plasma coagulation
Endoscopic resection
Gastrectomy
Neoplasms
Stomach

ABSTRACT

Backgrounds/aim: We aimed to evaluate the feasibility of endoscopic treatment for gastric epithelial neoplasm in the remnant stomach after distal gastrectomy and compared the clinical outcomes by tumor location and endoscopic treatment modality.
Methods: We reviewed the data of patients who underwent endoscopic treatment for gastric epithelial neoplasms in the remnant stomach after distal gastrectomy between January 1996 and August 2013. The treatments included endoscopic resection or argon plasma coagulation.
Results: Herein, 107 patients (median age, 65.1 years; 92 men) encompassing 117 cases of gastric neoplasms in the remnant stomach after distal gastrectomy were endoscopically treated. Forty of these lesions were located at anastomotic sites; they were treated with endoscopic resection in 29 cases (72.5%) and argon plasma coagulation in 11 cases (27.5%). For 77 lesions located on the non-anastomotic site, endoscopic resection was performed in 68 cases (88.4%) and argon plasma coagulation was performed in nine cases (11.7%; $p = 0.031$). The mean endoscopic resection duration was significantly longer in the anastomotic site group than in the non-anastomotic site group (43.6 vs. 26.3 min, $p = 0.018$). Recurrence was observed in five (12.8%) patients in the former and in one (1.3%) in the latter ($p = 0.015$); all the patients were successfully retreated with endoscopic resection or APC.
Conclusions: Endoscopic treatment for gastric epithelial neoplasm in a remnant stomach after distal gastrectomy is effective and safe. However, closely monitoring for recurrence should be conducted, particularly when the tumor is located at the anastomotic site.

1. Introduction

Gastric cancer is the fourth most prevalent form of cancer and the third leading cause of cancer-related deaths worldwide [1]. Early detection of gastric cancer and improvements in treatment modalities have enabled preservation of the stomach. However, patients with remnant stomach are at risk of developing subsequent metachronous gastric cancer, which occurs in 0.6%–2.9% cases [2].

Endoscopic resection (ER), which includes endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR), is a standard treatment for early gastric cancer (EGC) and poses minimal risk of lymph node metastasis [3–5]. Depending on the location of the lesion, ER in the remnant stomach can be technically challenging because of the limited working space and presence of fibrosis and staples under the suture line [6]. Some studies have reported on the use of ER for gastric neoplasms in the remnant stomach [6–10]. However, the evidence of its efficacy is still lacking.

Argon plasma coagulation (APC), a non-contact thermal method for tissue coagulation, includes applying a high-frequency electric current to the tissue using ionized argon gas [11,12]. APC can be an alternative to ER in high-risk patients [13]. APC can be used to treat lesions at postoperative anastomotic sites if the lesions do not elevate on injecting submucosal saline owing to fibrosis along the suture line. To our knowledge, detailed treatment outcomes of using APC in the remnant stomach after distal gastrectomy have not been reported yet.

To fill this gap in knowledge, we herein aimed to evaluate the feasibility of endoscopic treatment, including ER and APC, for gastric epithelial neoplasms and compare endoscopic treatment outcomes by the lesion site (anastomotic vs. non-anastomotic) and the endoscopic procedure used (ER vs. APC).

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https://doi.org/10.1016/j.dld.2018.11.030
1590-8658/

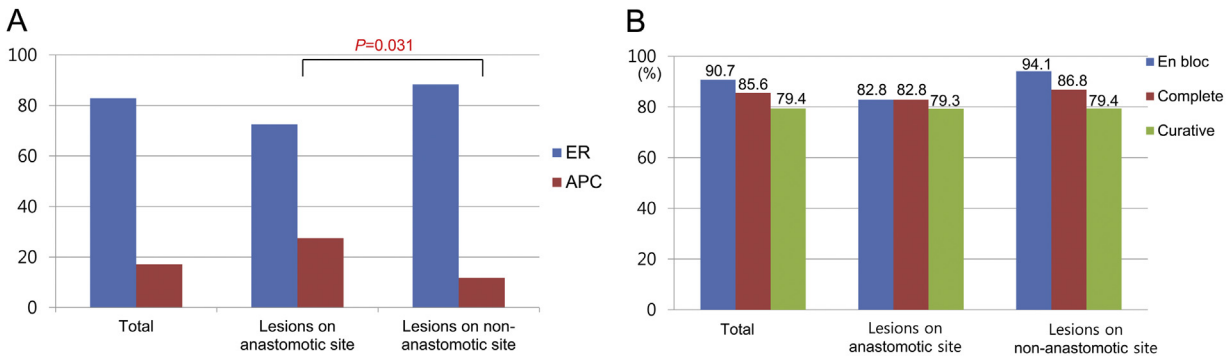

Fig. 1. (A) Endoscopic treatment modality in patients with remnant stomach after distal gastrectomy (B) *En bloc*, complete, and curative resection rates of patients who had undergone endoscopic resection (endoscopic mucosal resection or endoscopic submucosal dissection) for gastric epithelial neoplasms in the remnant stomach after distal gastrectomy.

2. Methods

2.1. Patients

We retrospectively reviewed the data of patients who underwent endoscopic treatment [ER (including EMR and ESD) or APC] for gastric epithelial neoplasms in the remnant stomach after distal gastrectomy at the Asan Medical Center, Seoul, Korea, between January 1996 and August 2013. Fig. 1 shows a flow chart of the study population. A total of 12,967 gastric lesions were treated with ER, or APC during the study period. Among these lesions, we identified 208 lesions in 191 patients with a remnant stomach. We excluded 60 patients with gastric polyps (67 polyps), two with carcinoid tumors, one who underwent proximal gastrectomy, one who underwent segment resection, three for whom endoscopic images were not available, and 17 who were using a gastric tube. Therefore, 107 patients having undergone distal gastrectomy and encompassing 117 gastric epithelial neoplasms were included: 51 low-grade dysplasia (LGD), 17 high-grade dysplasia (HGD), and 49 early gastric cancer (EGC) lesions. As for LGD lesions, all lesions could be defined endoscopically (Supplementary Fig. S1). Of the 117 neoplasms, 40 were located at anastomotic sites and 77 at non-anastomotic sites in the remnant stomach.

The ideal endoscopic treatment was chosen by an endoscopist. Although ER was the first treatment option considered widely, APC was the preferred treatment for some patients, including those at high risk of complications (e.g., perforation or severe bleeding), those with lesions which were technically challenging to treat using ER, and those in whom lesions did not lift on saline injection. Our study protocol was reviewed and approved by the institutional review board of the Asan Medical Center, Ulsan College of Medicine (IRB number S2017-0988-0001).

2.2. Endoscopic procedure and follow-up

Patients were sedated with midazolam (0.05 mg/kg i.v.) and pethidine (25 or 50 mg i.v.). Cardiorespiratory functions were continuously monitored during each procedure.

As mentioned earlier, ER comprised EMR or ESD. During EMR, after marking the lesion, an epinephrine-containing saline solution (epinephrine, 0.01 mg/mL) mixed with indigo carmine was injected. Then, circumferential incision and removal of the elevated mucosa was performed using an SD-9U-1 or SD-1U-1 snare (Olympus, Japan). For ESD, once the lesion was marked, marking dots were placed outside the margin of the lesion. A mixture of normal saline solution and indigo carmine with 1: 10,000 diluted epinephrine was injected into the submucosal layer. A needle–knife (MTW Endoskopie Co. Ltd., Wesel, Germany) or an insulated-tipped knife (Olympus) was used for making a circumferential mucosal incision around the tumor. Then, submucosal dissection was performed using an insulated-tipped knife (Olympus). Endoscopic hemostasis was performed using hemostatic forceps (FD-410LR; Olympus) or hemoclips if bleeding occurred or an exposed vessel was observed.

For APC (APC 300; Erbe Elektromedizin, Tuebingen, Germany), saline containing epinephrine (0.01 mg/mL) was injected into the submucosal layer; the lesion was ablated with APC. The gas flow rate was 1.8 L/min; the electrical current was set at 40, 60, or 80 W.

After endoscopic treatment, patients were examined by conventional esophagogastroduodenoscopy (EGD) at 3, 6, and 12 months postoperatively and annually thereafter. Patients with EGC were checked for extra-gastric recurrence using abdominal computed tomography, which was performed every 6 months for the 1st year and on an annual basis thereafter.

2.3. Definition

The anastomotic site was defined as including both the anastomotic ring (gastroduodenostomy or gastrojejunostomy) and the suture line on the lesser curvature side of the remnant stomach body. The macroscopic type of epithelial neoplasms was classified according to the Japanese Gastric Cancer Association criteria [14]. The degree of differentiation was classified according to the World Health Organization recommendations [15].

En bloc resection was defined as the resection of the entire lesion as a single piece without fragmentation. Complete resection was defined as histologically confirmed tumor resection with at least 0.5-mm deep margin and 2-mm lateral margin from the tumor periphery. If a tumor was resected in fragments but was found to have sufficient tumor-free margins on reconstruction of all pieces, the resection was still considered as complete resection. Curative resection was defined as complete resection of differentiated cancer with no lymphovascular invasion and the depth of tumor invasion being <500 μm from the muscularis mucosa.

The recurrence of epithelial neoplasm (cancer or dysplasia) at the resection site was defined as local recurrence. The procedure was timed from the beginning of making markings around the tumor to achieving complete hemostasis after the endoscopic treatment. Significant bleeding was defined as blood loss resulting in (1) clinical symptoms (melena or hematemesis), (2) decreased hemoglobin (>2 mg/dL), or (3) the need for transfusion or endoscopic hemostasis.

2.4. Statistical analysis

Continuous variables are shown as mean ± standard deviation (SD) or median (range). The anastomotic and non-anastomotic site

groups were compared for categorical variables by Pearson's chi-squared analysis and for continuous variables by a paired t-test. All tests of significance were two-tailed. p Values < 0.05 were considered to indicate statistical significance. Statistical analyses were performed using SPSS 21 Statistics for Windows (SPSS, Chicago, IL, USA).

3. Results

Baseline characteristics of the study population are shown in Table 1. The mean age of the 107 included patients was 65.1 years, and 86% patients were males. All patients had undergone distal gastrectomy for malignancy. The gastroduodenostomy to gastrojejunostomy ratio was 4.6:1. The median interval from distal gastrectomy to detect metachronous tumor was 41.9 months. Macroscopically, nine lesions (7.7%) were elevated, 106 (90.6%) were flat, and two (1.7%) were depressed.

3.1. Clinical outcomes based on tumor location

Table 2 shows pathologic features and procedure-related outcomes of patients by tumor location. The frequency of performing ER in the non-anastomotic site group was higher than in the anastomotic site group (88.4% vs. 72.5%, $p = 0.031$; Fig. 1). The mean ER procedure time in the anastomotic site group was significantly longer than it was in the non-anastomotic site group (41.9 vs. 27.2 min, $p = 0.043$).

Among the 97 lesions that were treated with EMR or ESD, *en bloc* resection was achieved in 24 (82.8%), complete resection in 24 (82.8%), and curative resection in 23 (79.3%) lesions in the anastomotic site group (Fig. 2). In the non-anastomotic site group, *en bloc* resection was achieved in 64 (94.1%, $p = 0.122$), complete resection in 59 (86.8%, $p = 0.753$), and curative resection in 54 lesions (79.4%, $p = 0.991$) (Fig. 2).

Table 1
Baseline characteristics of the study population.

Patients/lesions	107/117
Age (years), mean ± SD	65.1 ± 8.6
Sex (male/female), no.	92/15
Reason for distal gastrectomy, no. (%)	
Malignancy	107 (100)
High-grade dysplasia	2 (1.9)
Early gastric cancer	74 (69.1)
Advanced gastric cancer	31 (29.0)
Reconstruction, no. (%)	
Gastroduodenostomy	88 (82.2)
Gastrojejunostomy	19 (17.8)
Interval from previous surgery (months), median (range)	41.9 (4–180)
Tumor location, no. (%)	
Fundus	1 (0.9)
Body	72 (61.5)
Cardia	44 (37.6)
Lesion circumference, no. (%)	
Anterior wall	23 (19.7)
Greater curvature	15 (12.8)
Posterior wall	40 (34.2)
Lesser curvature	39 (33.3)
Morphological type, no. (%)	
0–I	9 (7.7)
0–IIa	87 (74.4)
0–IIb	10 (8.5)
0–IIc	9 (7.7)
0–IIa + IIc	2 (1.7)

SD, standard deviation; no., number.

In addition, we divided the groups according to histology (dysplasia vs. cancer), ER was more frequently performed in the cancer group than in the dysplasia group (95.9% vs. 7.3.5%, $p < 0.0001$). The mean endoscopic resection duration in the cancer group was significantly longer than it was in the dysplasia group (40.4 vs. 23.1 min, $p = 0.001$) (Supplementary Table S1).

Table 2
Clinical outcomes in patients with gastric epithelial neoplasms based on the tumor location.

	Total	Anastomotic site	Non-anastomotic site	p Value
Patients/lesions, no.	107/117	36/40	71/77	
Method of endoscopic treatment, no. (%)				0.036
EMR	41 (35.0)	9 (22.5)	32 (41.6)	
ESD	56 (47.9)	20 (50.0)	36 (46.8)	
APC	20 (17.1)	11 (27.5)	9 (11.7)	
Procedure duration of ER[a] (min)	31.5 ± 25.6	43.6 ± 35.4	26.3 ± 18.1	0.018
Longest tumor diameter (mm)	14.0 ± 9.0	15.4 ± 10.5	13.2 ± 8.2	0.212
Histology[b], no. (%)				0.288
Differentiated	45 (91.8)	16 (94.1)	29 (90.6)	
Undifferentiated	4 (8.2)	1 (5.9)	3 (9.4)	
Pathology of biopsy specimen, no. (%)				0.806
Low-grade dysplasia	55 (47.0)	19 (47.5)	36 (46.8)	
High-grade dysplasia	21 (18.0)	9 (22.5)	12 (15.6)	
Adenocarcinoma	37 (31.6)	10 (25.0)	27 (35.1)	
Signet ring cell carcinoma	2 (1.7)	1 (2.5)	1 (1.3)	
Atypical glandular proliferation	2 (1.7)	1 (2.5)	1 (1.3)	
Depth of invasion[a], no. (%)				0.146
Low-grade dysplasia	39 (40.2)	9 (31.0)	30 (44.1)	
High-grade dysplasia	11 (11.3)	4 (13.8)	7 (10.3)	
Mucosal cancer	33 (34.0)	13 (44.8)	20 (29.4)	
Submucosal cancer	14 (14.4)	3 (10.3)	11(16.2)	
En bloc resection[a]	88 (90.7)	24 (82.8)	64 (94.1)	0.122
Complete resection[a]	83 (85.6)	24 (82.8)	59 (86.8)	0.753
Curative resection[a]	77 (79.4)	23 (79.3)	54 (79.4)	0.991
Complication, no. (%)				
Bleeding	2 (1.7)	0 (0)	2 (2.6)	0.552
Local recurrence	6 (5.1)	5 (12.8)	1 (1.3)	0.015
Follow-up period (months), mean ± SD	54.6 ± 28.2	51.3 ± 25.8	56.4 ± 29.3	0.226

The anastomotic site group includes lesions on the anastomotic suture line of the remnant stomach body and the anastomotic ring.
APC, argon plasma coagulation; EMR, endoscopic mucosal resection; ER, endoscopic resection; ESD, endoscopic submucosal dissection; no., number; SD, standard deviation.
[a] Analysis of only patients who underwent endoscopic resection (EMR and ESD).
[b] Analysis of only patients with early gastric cancer.

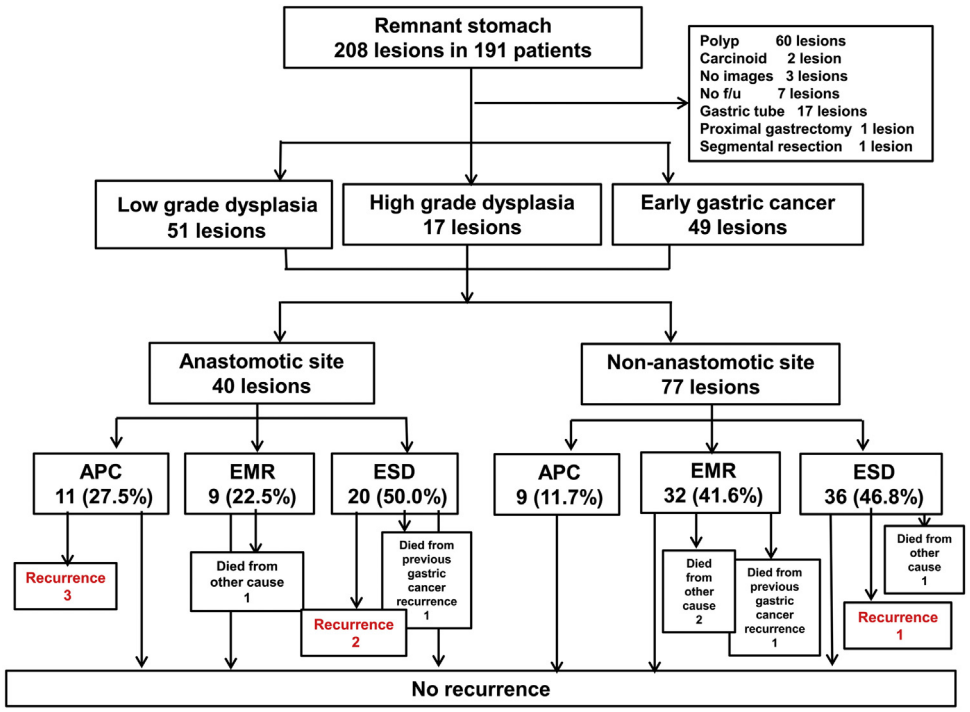

Fig. 2. Clinical courses of the study population.

Table 3
Treatment results for patients with gastric epithelial neoplasm in remnant stomach.

	En bloc resection	p Value	Complete resection	p Value	Curative resection	p Value
Tumor location		0.122		0.753		0.991
Anastomotic	24 (82.8)		24 (82.8)		23 (79.3)	
Non-anastomotic	64 (94.1)		59 (86.8)		54 (79.4)	
Treatment method		0.161		0.527		0.460
EMR	35 (85.4)		34 (82.9)		34 (82.9)	
ESD	53 (94.6)		49 (87.5)		43 (76.8)	
Histology		0.114		0.572		0.050
Low grade dysplasia	38 (97.4)		34 (87.2)		34 (87.2)	
High grade dysplasia	9 (81.8)		10 (90.9)		10 (90.9)	
Early gastric cancer	41 (87.2)		39 (83.0)		33 (70.2)	

Analysis of only patients who underwent endoscopic resection (EMR and ESD).
EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; no., number.

3.2. Outcomes of endoscopic resection

Table 3 shows the results of endoscopic resection in the study population. *En bloc* rate and complete resection rates were not significantly different according to tumor location (anastomotic vs. non-anastomotic), treatment method (EMR vs. ESD), and histology (LGD vs. HGD vs. EGC). As for curative resection rate, the rate of LGD and HGD showed higher than the rate of EGC (87.2%, 90.9% vs. 70.2%, $p = 0.050$).

3.3. Complications and recurrence

Table 4 showed the procedure related complications and recurrence in the study patients. Major bleeding occurred in two patients; one who had undergone EMR for a 7-mm lesion of low-grade dysplasia in a non-anastomotic area and one who had undergone ESD for a 20-mm lesion of low-grade dysplasia in a non-anastomotic area. Bleeding occurred within two days of endoscopy in both cases, and both patients were successfully treated with endoscopic hemostasis. There were no patients with perforation.

During a median follow-up of 54.6 months (range, 4–124 months), five patients (12.8%) in the anastomotic site group and one patient (1.3%) in the non-anastomotic site group had local tumor recurrence ($p = 0.017$). All patients with recurrence were successfully managed with APC or ER. Clinical courses of the study patients are shown in Fig. 3. Detailed data of patients who had local recurrence and had undergone non-curative resection are shown in Supplementary Tables S1 and S2.

3.4. Survival

The 3-year overall and 3-year disease-specific survival rates were 97.4% and 100% in the anastomotic site group and 95.6% and 100% in the non-anastomotic site group, respectively ($p = 0.555$). On the basis of the treatment modality used, the 3-year overall survival rates were 95.4% in the ER group and 100% in the APC group ($p = 0.319$). Among the five patients who died during the follow-up period, three died of unrelated malignant conditions, such as lung cancer or cholangiocarcinoma and two of gastric cancer recurrence. In those two patients, the initial gastric cancer was more advanced

Table 4
Procedure related complications and recurrence for patients with gastric epithelial neoplasms in remnant stomach.

	Bleeding	p Value	Recurrence	p Value
Tumor location, no (%)		0.546		0.017
Anastomotic	0 (0)		5 (12.5)	
Non-anastomotic	2 (2.6)		1 (1.3)	
Treatment method, no (%)		0.629		0.044
EMR	1 (2.4)		0 (0)	
ESD	1 (1.8)		3 (5.4)	
APC	0 (0)		3 (15.0)	
Histology, no (%)		0.280		0.945
Low grade dysplasia	2 (3.8)		3 (3.8)	
High grade dysplasia	0 (0)		2 (12.5)	
Early gastric cancer	0 (0)		2 (4.1)	

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; no., number; APC, argon plasma coagulation; no, number.

than the recurred metachronous gastric epithelial neoplasms in the remnant stomach.

4. Discussion

In the present study, we evaluated the feasibility and safety of endoscopic treatment for gastric epithelial neoplasms in the remnant stomach after distal gastrectomy. Treatment outcomes were compared for epithelial neoplasms located at anastomotic and non-anastomotic sites. In this study, 34.2% (40/117) of the gastric epithelial neoplasms in the remnant stomach were at the anastomotic site, and among the two techniques, ER (comprising EMR or ESD) was performed more frequently for lesions located at a non-anastomotic site than for those located at an anastomotic site. Selection of the ideal endoscopic treatment modality appears to be significantly influenced by the location of the lesion (i.e., whether the tumor involves suture lines). When a tumor located at the anastomotic site could not be lifted by a submucosal saline injection, planned EMR or ESD can be changed to APC because of the high risk of perforation.

For patients in whom ER was performed, the procedure time in the anastomotic site group was significantly longer than in the non-anastomotic site group (43.6 vs. 26.3 min, $p = 0.018$), which may be due to difficulty in performing ER for lesions at the anastomotic site. In a study on the outcomes of ESD in 33 patients with EGC in the remnant stomach, the procedure duration in the anastomotic site group was significantly longer than in the non-anastomotic site group (203 vs. 62.5 min, $p < 0.001$); this finding is consistent with our data [10]. In the current study, the overall *en bloc*, complete, and curative resection rates were 90.7%, 85.6%, and 79.4%, respectively, which are similar to results reported previously [7–9] and did not significantly differ between the two groups. Although it is technically challenging to perform ER of a tumor in the remnant stomach, particularly for lesions at the anastomotic site, we herein report appreciably high rates of *en bloc* and curative resection owing to the expertise of the experienced endoscopists who performed the procedures.

APC can be an alternative to ER in patients at high risk of bleeding or perforation or in those with a positive non-lifting sign after submucosal saline injection [13]. APC also has the advantage that it can be performed by less experienced gastrointestinal endoscopists. However, it has some limitations as well; specimens cannot be obtained for pathological evaluation after treatment [16], and there is a relatively higher incidence of local recurrence (4.0%–21.2%) [13,17–19]. In a previous study, we reported treatment outcomes of 71 patients who had undergone APC therapy for gastric epithelial neoplasms. In that study, the use of a higher power of 60 W or 80 W and submucosal saline injection before APC were the factors that reduced local recurrence [13]. These results are consistent with data in the current study, showing that lesions treated with 40 W power had a relatively higher recurrence rate than lesions treated with a 60 W or 80 W power regardless of the tumor location.

In this study, there were two patients with significant bleeding after ER; both these patients were successfully treated with endoscopic hemostasis. Perforation rates for ESD for gastric neoplasm in the remnant stomach were 1.4%–18.0% in previous studies [6,9,10]. However, there were no patients with perforation in this study. This is most likely due to APC being performed instead of ER in some patients to avoid perforation, particularly for lesions involving the anastomotic site. In a study reporting the result of ESD for EGC in the remnant stomach, three perforations occurred at the small intestine in the anastomotic site group with Billroth II reconstruction, and the authors cautioned that patients who undergo Billroth II should be treated with care [10].

Among 14 patients who had undergone non-curative resection, only three showed local recurrence during the median follow-up of 54.6 months. The following were the reasons for non-curative resection in our study: lateral margin positivity and a deep resection margin that could not be checked. These may have been caused by a coagulation effect, even if there were no residual tumor cells. All six patients who had undergone ER or APC and showed recurrence have been successfully managed with re-do endoscopic treatment during the follow-up. In our study, the 3-year overall and disease-specific survival rates were 96.2% and 100%, respectively. In a retrospective study that included 62 lesions in the gastric tube or remnant stomach, the 3-year overall and disease-specific survival rates were similar to our results (85.0% and 100%, respectively) [6].

In this study, we included the patients with visible LGD even though many cases of LGD could be closely followed without endoscopic treatment. However, there is discrepancy between forceps biopsy and endoscopic resected specimen and final pathologic diagnosis can be changed from LGD to HGD or EGC. In previous studies reporting discrepancy between endoscopic forceps biopsy and endoscopic resection in gastric epithelial neoplasm, the overall discrepancy rate ranged from 32–63% and after endoscopic resection, 24–63% LGD were diagnosed as HGD or carcinoma [20–23]. In the present study, the discrepancy rate between forceps biopsy and endoscopic resection was 14.4% (14/97). Among the 43 cases of LGD diagnosed with forceps biopsy and underwent endoscopic resection, 6 (14.0%) cases were upgraded as HGD or EGD with final pathology. Therefore, diagnosis based on forceps biopsy could be not sufficient for gastric LGD and we thought it is better to include patients with LGD for analysis European guidelines also recommended to perform endoscopic resection for endoscopically defined LGD lesion to obtain a more accurate histological diagnosis [24].

We would like to emphasize that careful follow-up with EGD after endoscopic treatment is essential for detecting local recurrence or metachronous lesions in the remnant stomach. Only early detection enables endoscopic treatment. Low resectability and high postoperative morbidity and mortality rates resulted in poor prognosis of patients with advanced remnant gastric cancer [25]. Studies on surgical resection of remnant gastric cancers reported high postoperative morbidity rates of 20%–42% and postoperative mortality rates of 0–12.5% [26]. In a study on 108 patients with gastric cancer in the remnant stomach after distal gastrectomy, outcomes for patients with non-early gastric stump cancer were poor, and lifelong annual follow-up EGD and strict surveillance for at least 10 years after the initial gastrectomy were recommended [25].

Our study has several limitations. First, because the endoscopic treatment modality was chosen by the performing endoscopist, selection bias could not be avoided. Second, complete remission was not confirmed in patients who had undergone APC with final specimen pathology; therefore, diagnostic discordance with the

biopsy specimen is possible. Despite these limitations, our study compared clinical outcomes over a relatively long follow-up duration, supporting the safety and feasibility of endoscopic treatments for gastric epithelial neoplasms in the remnant stomach. Our results suggest that APC can be an acceptable alternative treatment to ER, with particularly favorable clinical outcomes for tumors located at the anastomotic site.

In conclusion, endoscopic treatment is safe and effective for gastric epithelial neoplasms in the remnant stomach. APC seems like a useful alternative to ER for lesions located at anastomotic sites. Close endoscopic monitoring is mandatory, particularly for tumors located at anastomotic sites; patients with local recurrence found during follow-up endoscopy can be managed with repeat endoscopic treatment.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.11.030.

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