Clinicopathological Characteristics and Endoscopic Features of Early Gastric Cancers Diagnosed After Helicobacter pylori Eradication: A Retrospective Study

Hideki Ishibashi
Fukuoka University Faculty of Medicine

Hidetoshi Takedatsu
Fukuoka University Faculty of Medicine

Taro Tanabe
Fukuoka University Faculty of Medicine

So Imakiire
Fukuoka University Faculty of Medicine

Hiroki Matsuoka
Fukuoka University Faculty of Medicine

Hideki Yasuda
Fukuoka University Faculty of Medicine

Hideto Sakisaka
Fukuoka University Faculty of Medicine

Satoshi Matsuoka
Fukuoka University Faculty of Medicine

Yoshiyuki Kayashima
Fukuoka University Faculty of Medicine

Nobuaki Kuno
Fukuoka University Faculty of Medicine

Koichi Abe
Fukuoka University Faculty of Medicine

Sadahiro Funakoshi
Fukuoka University Faculty of Medicine

Fumihito Hirai (✉ fuhiral@cis.fukuoka-u.ac.jp)
https://orcid.org/0000-0002-5493-5675

Research article
Abstract

Background: Helicobacter pylori (H. pylori) infection is an important risk factor for developing gastric cancer. However, even after H. pylori eradication, early gastric cancer (EGC) can develop. We elucidated the characteristics of EGCs diagnosed after H. pylori eradication.

Methods: Thirty-six EGCs in 32 patients diagnosed after H. pylori eradication were defined as the eradication group (H. pylori-EG). The clinicopathological and endoscopic features were compared with those of 156 EGCs in 140 patients in the H. pylori-positive group (H. pylori-PG). Twenty-nine EGC lesions in the H. pylori-EG were further divided into two subgroups: the first included six lesions of none to mild atrophic mucosa around the EGC, and the second included 23 lesions of moderate to severe atrophic mucosa around the EGC. We compared them between the two subgroups.

Results: Endoscopic features of EGCs in the H. pylori-EG were characterized as small (P = 0.049) and of the depressed type (P = 0.022) compared with those in the H. pylori-PG. EGCs in the H. pylori-EG were detected on the upper region of the stomach more frequently than those in the H. pylori-PG (P = 0.002). As for submucosal EGCs in the H. pylori-EG, it was more likely to be seen in the mild atrophic mucosa subgroup (4/6, 67%) compared to the moderate to severe atrophic gastric mucosa subgroup (1/23, 4%) (P = 0.003).

Conclusions: EGCs after H. pylori eradication were characterized as small and of the depressed type. Submucosal invasive EGCs developed more frequently in the none to mild atrophic mucosa after H. pylori eradication. Therefore, careful patient follow-up is important after H. pylori eradication.

Background

The infection with Helicobacter pylori (H. pylori) was classified as a carcinogen of gastric cancer by the World Health Organization in 1994. In patients with early gastric cancer (EGC) who underwent endoscopic resection, EGCs were detected in H. pylori-positive patients at a significantly higher rate than in H. pylori-eradication patients [1]. In a multicenter randomized controlled trial in Japan, the incidence of metachronous cancer was 14.1 cases per 1,000 person-years in the H. pylori-eradication group and 40.5 cases per 1,000 person-years in the no eradication group (hazard ratio 0.339, 95% CI 0.157–0.729, P = 0.003) [2]. The effectiveness of H. pylori eradication was proved by the decrease in the incidence of gastric cancer.

However, EGCs were sometimes detected after H. pylori eradication. Four previous studies showed the clinicopathological characteristics and endoscopic features of 239 EGCs after H. pylori eradication [3-6]. The median size of EGCs was 12.8 mm and the locations were upper (41 lesions, 17%), middle (109 lesions, 44%), and lower (94 lesions, 39%) regions of the stomach. Endoscopic examination revealed that 34 were elevated lesions (18%) and 152 (82%) were depressed-type lesions [3-5]. Regarding depth of invasion, 206 (86%) were intramucosal lesions and 33 (14%) were submucosal invasive lesions [3-6].
EGCs after *H. pylori* eradication were histopathologically characterized as small and depressed lesions with low cell proliferation and gastric mucin phenotypes [3-7].

Because there are only several reports concerning gastric cancer after *H. pylori* eradication, we conducted a retrospective study investigating the clinicopathological characteristics and endoscopic features of EGCs diagnosed after *H. pylori* eradication.

**Methods**

**Study Subjects**

The study was conducted at Fukuoka University from January 2009 to January 2018. The Medical Ethics Committee of Fukuoka University approved this study (IRB number: U20-01-011).

1. **Primary Endpoint**

Primary endpoint of this study to investigate the association between the clinicopathological characteristics and endoscopic features of EGCs diagnosed after *H. pylori* eradication. We enrolled 397 consecutive patients who underwent endoscopic submucosal dissection (ESD) treatment of their EGC. Of these, 225 patients were excluded as follows: 89 patients were not examined for *H. pylori* status; in 124 patients, *H. pylori* was not detected, and these patients did not have a past history of receiving *H. pylori* eradication therapy; and in another 12 patients, EGCs were resected using ESD within 1 year after *H. pylori* eradication. The remaining 172 patients were divided into two groups: An *H. pylori*-eradication group (*H. pylori*-EG) that comprised 36 EGCs in 32 patients who had undergone *H. pylori* eradication therapy more than 1 year before and on whom ESD was performed to treat their EGC, and an *H. pylori*-positive group (*H. pylori*-PG; the control group) that comprised 156 EGCs in 140 patients with an active *H. pylori* infection and on whom ESD was performed to treat their EGC (Fig. 1).

2. **Secondary Endpoint**

It remains unclear whether the mucosal atrophy affect the characteristics of EGC after eradication of *H. pylori*. Therefore, we compared the clinicopathological characteristics and endoscopic features between the two groups classified by the degree of gastric mucosal atrophy in the *H. pylori*-EG group. To investigate the association between EGC characteristics and the degree of mucosal atrophy after *H. pylori* eradication, 29 lesions of EGC in the *H. pylori*-EG group, in which the degree of mucosal atrophy had been confirmed in ESD specimens, were divided into two subgroups according to endoscopic and histological examinations. The mild atrophic mucosa subgroup comprised 6 lesions that were none to mild atrophic mucosa around the EGC, and the moderate to severe atrophic mucosa subgroup comprised 23 lesions that were moderate to severe atrophic mucosa around the EGC (Fig. 1).

**Evaluation of *H. pylori* status**
Evaluation of *H. pylori* eradication treatment was based on the $^{13}$C-urea breath test (UBT) or serum immunoglobulin (Ig) G antibody test (E-plate, Eiken, Tokyo, Japan) and on histological assessment using endoscopic biopsy specimens. When both examinations were negative, we determined that *H. pylori* had been eradicated. One hundred and forty patients in the control group were *H. pylori*-positive based on UBT or serum IgG antibody and histological assessment, and had no history of receiving *H. pylori* eradication therapy.

**Clinicopathological Assessment**

Clinicopathological findings such as size, location, macroscopic type, histological type, and depth of tumor invasion were reviewed for gastric carcinomas according to both the Japanese [8] and World Health Organization classification [9]. The extent and degree of atrophic gastritis was evaluated endoscopically and histologically and classified into six categories according to the Kimura and Takemoto classification system (C-1 to O-3) [10].

**Endoscopic Procedures**

Endoscopic examinations were performed by three experienced endoscopists (H.I, T.T, N.K) using a magnifying endoscope (GIF-H260Z, H290Z, Olympus Medical System, Tokyo, Japan). We used structural enhancement levels of A-8 for conventional endoscopy and B-8 for narrow-band imaging with magnifying endoscopy (NBI-ME). NBI-ME for diagnosing EGC was performed using a systematic classification system based on microvascular patterns and microsurface patterns (the "VS classification"). An irregular microvascular pattern (IMVP) and/or an irregular microsurface pattern (IMSP) with clear demarcation lines are the hallmarks of EGC [11]. EGCs were confirmed using histopathological findings of biopsies and ESD samples.

**Statistical Analysis**

Data were analyzed using JMP® 15 statistical software (SAS Institute Inc., Cary, NC, USA). Continuous variables between two groups were evaluated using the Mann–Whitney $U$ test. Categorical variables were evaluated using the chi-squared test. $P$ values of <0.05 were considered statistically significant.

**Results**

**Clinicopathological characteristics and endoscopic features of early gastric cancers of the *H. pylori*-eradication group and the *H. pylori*-positive group**

Clinicopathological characteristics and endoscopic features EGCs of the *H. pylori*-EG and the *H. pylori*-PG are summarized in Table 1. There were 36 EGCs in 32 patients in the *H. pylori*-EG and 156 EGCs in 140 patients in the *H. pylori*-PG. The median patient age in the *H. pylori*-EG (68.1±7.3) was significantly younger than that of patients in the *H. pylori*-PG (71.5±8.7) ($P = 0.038$). The median lesion size in the *H. pylori*-EG (12.7±8.2 mm) was significantly smaller than that in the *H. pylori*-PG (16.5±10.8 mm) ($P =$
EGCs were frequently detected on the upper region of the stomach in six of 36 patients in the *H. pylori*-EG (17%) compared with five of 156 in the *H. pylori*-PG (3%; *P* = 0.002). Regarding macroscopic features, elevated lesions were more frequent in 57 of 156 patients in the *H. pylori*-PG (36%) compared with six of 36 in the *H. pylori*-EG (17%; *P* = 0.022). Depressed lesions were more frequent in 30 of 36 patients in the *H. pylori*-EG (83%) compared with 99 of 156 in the *H. pylori*-PG (64%; *P* = 0.022). Close type-3 in extent of atrophic gastritis according to Kimura and Takemoto classification system [10] was more frequent in the *H. pylori*-EG (8/36: 22%) compared with the *H. pylori*-PG (9/156: 6%; *P* = 0.0002). Open type-1 was more frequent in the *H. pylori*-PG (67/156: 43%) compared with the *H. pylori*-EG (6/36: 17%; *P* = 0.0002). EGCs after *H. pylori* eradication were characterized by features of the small and depressed type, and frequently detected on the upper region of the stomach compared with EGCs in the *H. pylori*-PG. In histological findings such as histologic type, depth of invasion, and lymphatic and venous invasion, there were no differences between the two groups.

**Association between characteristics of early gastric cancers and the degree of mucosal atrophy in the *H. pylori*-eradication group**

Clinicopathological characteristics and endoscopic features of EGCs of the mild atrophic gastric mucosa subgroup and the moderate to severe atrophic gastric mucosa subgroup within the *H. pylori*-EG are summarized in Table 2. Table 2 shows that six lesions (21%) were in the mild atrophic mucosa subgroup and 23 lesions (79%) were in the moderate to severe atrophic mucosa subgroup. Three of 6 mild atrophic subgroup (50%) had none atrophic mucosa around EGC. There were no significant differences in age, interval term from the eradication of *H. pylori* to the detection of the EGC, location, size, macroscopic finding, histologic type, or lymphatic and venous invasion between the two subgroups. In the moderate to severe atrophic subgroup, there were more males than in the mild atrophic mucosa subgroup (*P* = 0.02). Regarding depth of invasion, submucosal invasive EGC lesions were detected in four of six lesions (67%) in the mild atrophic mucosa subgroup and only 1 of 23 lesions (4%) in the severe atrophic mucosa subgroup (*P* = 0.003). Three of 4 submucosal invasive EGC lesions (75%) in mild atrophic subgroup had none atrophic mucosa around EGC.

**Median interval from the eradication of *H. pylori* to the detection of EGC**

In the *H. pylori*-EG, EGCs were detected 1–17 years (median, 4.6 years) following *H. pylori* eradication. In the mild atrophic gastric mucosa subgroup within the *H. pylori*-EG, the median interval from eradication therapy to detection of an EGC was 5.3 years (1–17 years). In the moderate to severe atrophic gastric mucosa subgroup, the median interval was 4.3 years (1–17 years). Median intervals were not significantly different between the two subgroups (Fig. 2). This result showed that there was no significant association between the duration of EGC incidence and the degree of mucosal atrophy.

**Submucosal invasive early gastric cancer in the *H. pylori*-EG group**

The clinicopathological characteristics and endoscopic features of submucosal invasive five EGCs in the mild atrophic gastric mucosa subgroup and moderate to severe atrophic mucosa subgroup within the *H.
pylori-EG are summarized in Table 3. Endoscopic features of EGCs in all cases showed a flattened and extended appearance when the entire stomach wall was distended with a high volume of air. Therefore, patients were diagnosed with intramucosal gastric cancer because they were negative for the non-extension sign [12]. Three cases (case 1, 3, 4) had none atrophic mucosa around EGC. Endoscopic and pathological findings of cases 1 and 4 are shown in Figures 3 and 4, respectively. In case 1, upper gastrointestinal (GI) endoscopy revealed a reddish small elevated lesion on the upper position of the gastric cardia (Fig. 3a). NBI-ME revealed a regular microsurface pattern and an absent microvascular pattern (Fig. 3b). The tumor was successfully removed en bloc using the ESD method (Fig. 3c). The resected specimen was evaluated histopathologically and revealed a well differentiated tubular adenocarcinoma invading into the submucosa (SM1) (Fig. 3d), none atrophic mucosa around EGC (Fig. 3e). In case 4, upper GI endoscopy revealed a reddish small depressed lesion on the upper position of the gastric cardia (Fig. 4a, b). The tumor was successfully removed en bloc using the ESD method (Fig. 4c). Histopathological examination revealed a well-differentiated tubular adenocarcinoma invading into the submucosa (SM2) and none atrophic mucosa around EGC (Fig. 4d).

**Discussion**

Because a meta-analysis of clinical studies indicated that gastric cancers occurred even after *H. pylori* eradication [4, 13, 14], it is important to recognize the clinical and histological characteristics of gastric cancers detected after *H. pylori* eradication for making the appropriate diagnosis and treatment. A previous report described 16 gastric cancers detected after *H. pylori* eradication that were characterized by a noncardiac location and less than 20 mm in size with depressed type features [15]. Furthermore, 96 gastric cancers detected after *H. pylori* eradication had endoscopic features of a depressed type and were small in size compared with *H. pylori*-positive cancers [4]. Gastric cancers detected after *H. pylori* eradication were characterized by a small size, a depressed type, and a lower Ki-67 labeling index compared with *H. pylori*-positive gastric cancers [3]. Likewise, the *H. pylori*-EG had more frequent small lesions and depressed types compared with the *H. pylori*-PG ($P = 0.049$, $P = 0.022$) in our study. The current study also showed that the features of EGC after *H. pylori* eradication were characterized as small lesions of the depressed type.

The prevalence of gastric cancers located on the upper region of the stomach was higher in the eradication group compared with the no eradication group, which suggests that gastric cancer developed on the upper region of the stomach after *H. pylori* eradication [5]. In our study showed the same tendency, EGCs were detected more frequently on the upper region of the stomach in the *H. pylori*-EG compared with the *H. pylori*-PG ($P = 0.002$). Hence, it is necessary to perform careful examination of the upper region of the stomach using upper GI endoscopy after treating a patient with *H. pylori* eradication therapy.

Several studies showed that patients with gastric cancer detected after eradication of *H. pylori* had severe atrophic gastritis [15, 16]. Atrophy of gastric mucosa in the antrum, angle, and corpus, and intestinal metaplasia in the lesser curvature of the corpus showed significant improvement during the 10-year period after eradication therapy. Therefore, the improvement of gastric atrophy and intestinal metaplasia
were associated with a reduction in gastric cancer occurrence [17]. However, the risk of developing a diffuse-type gastric cancer increases over time in patients with mild to moderate gastric atrophy before *H. pylori* eradication [18]. In this study, six of 29 cases (21%) were none to mild atrophic gastritis around the gastric cancer that occurred after *H. pylori* eradication. Our result strongly suggested that there was an incidence risk of EGC even in patients with none to mild atrophic gastritis after *H. pylori* eradication, although the incidence risk of EGC in patients with none to mild atrophic gastritis was lower than in those with severe atrophic gastritis.

Recently, several studies reported that there were cases of submucosal invasive EGCs after *H. pylori* eradication. In 162 patients with *H. pylori* eradication and non-*H. pylori* eradication, submucosal invasive EGCs were detected more frequently in the *H. pylori*-eradication group (13/81 patients, 16%) than in the non-*H. pylori*-eradication group (4/81 patients, 4.9%; *P* = 0.021) [19]. The submucosal invasive gastric cancer tended to be more frequent in the *H. pylori*-EG (18%) than in the non-*H. pylori*-EG (8%; *P* = 0.051) [4]. We described four cases of submucosal invasive EGCs with none to mild atrophic gastric mucosa after *H. pylori* eradication therapy. They were endoscopically diagnosed as intramucosal gastric cancer because of a negative non-extension sign as shown in case presentation [12]. Despite none to mild atrophy after *H. pylori* eradication, it is necessary to follow up using GI endoscopy because of the possibility of EGC and the high risk of invasive cancer.

A 9-year prospective study in Japan showed that 20 (1.1%) gastric cancers were diagnosed in 1,787 patients who underwent *H. pylori* eradication therapy. Of these 20 gastric cancers, 16 (80%) were diagnosed within 4 years after *H. pylori* eradication [15]. Previous studies reported that the median intervals from *H. pylori* eradication therapy to detection of gastric cancers were 2.6 years (range 0.8–11 years) [3], 4.1 years (1–15 years) [4], and 3 years (0.5–15 years) [5]. In this study, the median interval was 4.6 years (1–17 years). In the mild atrophic gastric mucosa subgroup of the *H. pylori*-EG, the median interval was 5.3 years (1–17 years). In the moderate to severe atrophic gastric mucosa subgroup, the median interval was 4.3 years (1–17 years). We suggested that upper GI endoscopic examination should be performed in patients in whom *H. pylori* had been eradicated for at least 6 years, regardless of the degree of atrophic mucosa. However, few cases of EGC were detected 15 or 17 years after *H. pylori* eradication therapy. Endoscopic surveillance should be continued beyond 10 years after *H. pylori* eradication regardless of the degree of gastric mucosal atrophy [18].

**Conclusions**

Our single-center study revealed that EGCs after *H. pylori* eradication were characterized endoscopically with features of small and depressed lesions and invasive carcinogenesis in the none to mild atrophic mucosa. Therefore, we should perform careful follow-up with upper GI endoscopic examination after *H. pylori* eradication, with special attention to small and depressed type gastric cancer for at least six years, but not more than 15 or 20 years. This study had several limitations. The study was retrospective and conducted at a single center. Because there are few reports that evaluate EGCs after *H. pylori* eradication,
it will be necessary to perform a prospective study across multiple patient populations and ethnic groups in the future.

**Abbreviations**

*H. pylori*. *Helicobacter pylori*, EGC: Early gastric cancer, ESD: Endoscopic submucosal dissection UBT: $^{13}$C-Urea breath test, NBI-ME: Narrow-band imaging with magnifying endoscopy IMVP: Irregular microvascular pattern, IMSP: Irregular microsurface pattern, GI: Gastrointestinal

**Declarations**

**Ethics approval and consent to participate**

This study conducted in accordance with the ethical standards of the declaration of Helsinki. This study protocol was approved by the Human Ethics Review Committee of Fukuoka University, Japan (IRB number: U20-01-011). Informed consent to participate this study was obtained from all patients in orally. The procedure for oral consent was approved by the ethics committee.

**Consent for publication**

Not applicable.

**Availability of date and materials**

The datasets used and analyzed in the current study are available from the corresponding author on reasonable request.

**Competing interests**

The author declare that they have no competing interests.

**Funding**

This study received no financial support.

**Author’s contributions**

HI and FH designed the research. HI, TT, SI, HM, HY, HS, SM, YK, NK, KA, SF performed research. HI, TT performed statistical analysis. HI, HT and FH wrote the paper. All authors read and approved the final manuscript.

**Acknowledgements**

We thank Mark Abramovitz, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.
References

1. Uemura N, Mukai T, Okamoto S, et al. Effect of Helicobacter pylori eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. Cancer Epidemiol Biomarkers Prev. 1997;6:639-42.

2. Fukase K, Kato M, Kikuchi S, Japan Gast Study Group, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomized controlled trial. Lancet. 2008;372:392-7.

3. Yamamoto K, Kato M, Takahashi M, et al. Clinicopathological analysis of early-stage gastric cancers detected after successful eradication of Helicobacter pylori. Helicobacter. 2011;16:210-6.

4. Maehata Y, Nakamura S, Esaki M, et al. Characteristics of Primary and Metachronous Gastric Cancers Discovered after Helicobacter pylori Eradication: A Multicenter Propensity Score Matched Study. Gut and Liver. 2017;11:628-34.

5. Horiguchi N, Tahara T, Kawamura T, et al. Distinct Clinic-Pathological Features of Early Differentiated-Type Gastric Cancers after Helicobacter pylori Eradication. Gastroenterology Research and Practice. 2016;8230815. doi: 10.1155/2016/8230815

6. Sakitani K, Nishizawa T, Arita M, et al. Early detection of gastric cancer after Helicobacter pylori eradication due to endoscopic surveillance. Helicobacter. 2018;23(4):e12503.

7. Matsuo T, Ito M, Tatsugami M, et al. Gastric cancer development after Helicobacter pylori eradication therapy: a new form of gastric neoplasia. Digestion. 2012;85:61-7.

8. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma, 3rd English Edition. Gastric Cancer. 2011;14:101-12.

9. Lauwers GY, Carneiro F, Graham DY, et al. Gastric carcinoma, In: Bosman FT, Carnerio F, Hruban PH, Theise ND, editors. WHO Classification of tumors of the digestive system. 4th ed. Lyon: IRAC Press, 2010: p. 48-58.

10. Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. Endoscopy. 1969;3:87-97.

11. Yao K, Anagnostopoulos GK, Ragunath K. Magnifying endoscopy for diagnosing and delineating early gastric cancer. Endoscopy. 2009;41:462-7.

12. Nagahama T, Yao K, Imamura K, et al. Diagnostic performance of conventional endoscopy in the identification of submucosal invasion by early gastric cancer: the “non-extension sign” as a simple diagnostic marker. Gastric Cancer. 2017;20:304-13.

13. Choi J, Kim SG, Yoon H, et al. Eradication of Helicobacter pylori after endoscopic resection of gastric tumors does not reduce incidence of metachronous gastric carcinoma. Clin Gastroenterol Hepatol. 2014;12:793-800.

14. Yoon SB, Park JM, Lim CH, Cho YK, Choi MG. Effect of Helicobacter pylori eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis. Helicobacter. 2014;19:243-8.
15. Kamada T, Hata J, Sugiu K, et al. Clinical features of gastric cancer discovered after successful eradication of *Helicobacter pylori*: results from a 9-year prospective follow-up study in Japan. Aliment Pharmacol Ther. 2005;21:1121-6.

16. Take S, Mizuno M, Ishiki K, Nagahara Y, Yoshida T, Yokota K, et al. Baseline gastric mucosal atrophy is a risk factor associated with the development of gastric cancer after *Helicobacter pylori* eradication therapy in patients with peptic ulcer diseases. J Gastroenterol. 2007;42 Suppl 17:21–7.

17. Kodama M, Murakami K, Okimoto T, et al. Ten-year prospective follow-up of histological changes at five points on the gastric mucosa as recommended by the updated Sydney system after *Helicobacter pylori* eradication. J Gastroenterol. 2012;47:394-403.

18. Take S, Mizuno M, Ishiki K, et al. Risk of gastric cancer in the second decade of follow-up after *Helicobacter pylori* eradication. J Gastroenterol. 2020;55:281-8.

19. Hata K, Ito M, Kotachi T, et al. Gastric Cancer with Submucosal Invasion after Successful *Helicobacter pylori* Eradication: A Propensity Score-Matched Analysis of Patients with Annual Patient Endoscopic Survey. Digestion. 2019;99(1):59-65.

**Tables**
Table 1.
Clinicopathological characteristics and endoscopic features of EGCs of the *H. pylori*-EG and the *H. pylori*-PG.

|                                      | Total            | *H. pylori*-EG | *H. pylori*-PG | P value |
|--------------------------------------|------------------|----------------|----------------|---------|
| No. of patients (lesions)            | 172 (192)        | 32 (36)        | 140 (156)      |         |
| Median age (range)                   | 69.8±8.0 (49–93) | 68.1±7.3 (52–85) | 71.5±8.7 (49–93) | 0.038   |
| Male: female                         | 141 : 31         | 26 : 6         | 115 : 25       | NS      |
| Size (diameter), mm                  | 15.7±10.4        | 12.7±8.2       | 16.5±10.8      | 0.049   |
| Location                             |                  |                |                |         |
| Upper                                | 11 (6%)          | 6 (17%)        | 5 (3%)         | 0.002   |
| Middle                               | 97 (51%)         | 20 (55%)       | 77 (49%)       |         |
| Lower                                | 84 (43%)         | 10 (28%)       | 74 (48%)       |         |
| Macroscopic type                     |                  |                |                |         |
| Elevated type                        | 63 (33%)         | 6 (17%)        | 57 (36%)       | 0.022   |
| Depressed type                       | 129 (67%)        | 30 (83%)       | 99 (64%)       |         |
| Histology                            |                  |                |                |         |
| Differentiated type                  | 183 (95%)        | 34 (94%)       | 149 (96%)      | NS      |
| Undifferentiated type                | 3 (2%)           | 1 (3%)         | 2 (1%)         |         |
| Mixed type                           | 6 (3%)           | 1 (3%)         | 5 (3%)         |         |
| Depth of invasion                    |                  |                |                |         |
| Mucosa                               | 160 (83%)        | 30 (83%)       | 130 (83%)      | NS      |
| Submucosa                            | 32 (17%)         | 6 (17%)        | 26 (17%)       |         |
| Ulceration or scar                   | 15 (8%)          | 2 (6%)         | 13 (8%)        | NS      |
| Lymphatic invasion                   | 6 (3%)           | 0              | 6 (4%)         | NS      |
| Venous invasion                      | 14 (7%)          | 1 (3%)         | 13 (8%)        | NS      |
| Extent of atrophic gastritis         |                  |                |                |         |
| C-1                                  | 6 (3%)           | 3 (8%)         | 3 (2%)         | 0.0002  |
| C-2                                  | 9 (5%)           | 2 (6%)         | 7 (4%)         |         |
| C-3                                  | 17 (9%)          | 8 (22%)        | 9 (6%)         |         |
| O-1                                  | 73 (38%)         | 6 (17%)        | 67 (43%)       |         |
|     | O-2  | O-3  |     |
|-----|------|------|-----|
|     | 50 (26%) | 14 (39%) | 36 (23%) |
|     | 37 (19%) | 3 (8%) | 34 (22%) |

EGCs: early gastric cancers, *H. pylori*-EG: *Helicobacter pylori*-eradication group
*H. pylori*-PG: *Helicobacter pylori*-positive group
Table 2.
Clinicopathological characteristics and endoscopic features of two groups in the *H. pylori*-EG.

|                          | Total          | Mild atrophic gastric mucosa group | Moderate to severe atrophic gastric mucosa group | P value |
|--------------------------|----------------|-----------------------------------|------------------------------------------------|---------|
| No. of lesions           | 29             | 6 (21%)                           | 23 (79%)                                       |         |
| Median age (range)       | 69.8 (61–85)   | 71.7 (65–75)                      | 69.3 (61–85)                                   | NS      |
| Male: female             | 25: 4          | 3 : 3                             | 22 : 1                                         | 0.02    |
| Location                 |                |                                   |                                                |         |
| Upper                    | 4 (14%)        | 2 (33%)                           | 2 (9%)                                         | NS      |
| Middle                   | 16 (55%)       | 3 (50%)                           | 13 (56%)                                       |         |
| Lower                    | 9 (31%)        | 1 (17%)                           | 8 (35%)                                        |         |
| Macroscopic type         |                |                                   |                                                |         |
| Elevated type            | 5 (17%)        | 1 (17%)                           | 4 (17%)                                        | NS      |
| Depressed type           | 24 (83%)       | 5 (83%)                           | 19 (83%)                                       |         |
| Size (diameter), mm      | 13.4±8.8       | 9.8±4.3                           | 14.3±9.5                                       | NS      |
| Histology                |                |                                   |                                                |         |
| Differentiated type      | 28 (97%)       | 5 (83%)                           | 23 (100%)                                      | NS      |
| Undifferentiated type    | 1 (3%)         | 1 (17%)                           | 0                                              |         |
| Depth of invasion        |                |                                   |                                                |         |
| Mucosa                   | 24 (83%)       | 2 (33%)                           | 22 (96%)                                       | 0.003   |
| Submucosa                | 5 (17%)        | 4 (67%)                           | 1 (4%)                                         |         |
| Ulceration or scar       | 1 (3%)         | 0                                 | 1 (4%)                                         | NS      |
| Lymphatic invasion       | 0              | 0                                 | 0                                              | NS      |
| Venous invasion          | 1 (3%)         | 1 (17%)                           | 0                                              | NS      |

EGCs: early gastric cancers, *H. pylori*-EG: *Helicobacter pylori*-eradication group
Table 3.
Clinicopathological characteristics and endoscopic features of submucosal invasive five EGCs in the *H. pylori*-EG group.

| Case  | Age  | Gender | Time after *H. pylori* eradication, yrs. | Location | Degree atrophic mucosa around EGC | Macroscopic type | Size (diameter), mm | Histology | Depth of invasion | Ulceration or scar | Lymphatic invasion | Venous invasion | Demarcation line | IMVP | IMSP | Treatment |
|-------|------|--------|----------------------------------------|----------|---------------------------------|-----------------|---------------------|-----------|------------------|-------------------|------------------|---------------|-----------------|--------|------|-----------|
| 1     | 75   | M      | 5                                      | U        | none                            | elevated type   | 5                   | differentiated type | SM1       | negative         | negative          | negative          | negative       | absent          | absent | absent | ESD       |
| 2     | 65   | F      | 2                                      | M        | mild                            | depressed type  | 15                  | differentiated type | SM2       | negative         | negative          | negative          | negative       | present         | present | present | ESD       |
| 3     | 77   | F      | 6                                      | M        | none                            | depressed type  | 15                  | undifferentiated type | SM1       | negative         | negative          | negative          | positive       | present         | present | present | ESD       |
| 4     | 70   | F      | 4                                      | U        | none                            | elevated type   | 8                   | differentiated type | SM3       | negative         | negative          | negative          | positive       | present         | present | present | ESD       |
| 5     | 66   | M      | 2                                      | M        | severe                          | depressed type  | 12                  | differentiated type | SM1       | positive          | positive          | negative          | positive       | present         | present | present | ESD       |

EGC: early gastric cancer, *H. pylori*-EG: *Helicobacter pylori*-eradication group, SM: submucosal, IMVP: irregular microvascular pattern

IMSP: irregular microsurface pattern, ESD: endoscopic submucosal dissection
# Figures

## Figure 1

397 Patients with EGC treated by ESD

- 225 Excluded
  - 89 Lack of investigation of *H. pylori* infection
  - 124 *H. pylori*-negative without history of eradication
  - 12 Underwent ESD within 1 yr after *H. pylori* eradication

172 Study Subjects

32 *H. pylori*-eradicated group
- 36 EGCs in 32 patients undergone ESD more than 1 yr after *H. pylori* eradication

140 *H. pylori*-positive group
- 156 EGCs in 140 *H. pylori*-positive patients

7 Excluded No evaluate degree atrophic mucosa around EGC

6 mild atrophic mucosa subgroup

23 moderate to severe atrophic mucosa subgroup

EGC: early gastric cancer, ESD: endoscopic submucosal dissection, *H. pylori*: *Helicobacter pylori*
Figure 2

Median interval from the eradication of H. pylori to the detection of EGC. In the mild atrophic gastric mucosa subgroup in the H. pylori-EG, the median interval from eradication therapy to the detection of gastric cancer was 5.3 years (1–17 years). In the moderate to severe atrophic gastric mucosa subgroup, the median interval was 4.3 years (1–17 years). Median intervals were not significantly different between the two subgroups.
Case 1 of submucosal invasive early gastric cancer in the mild atrophic gastric mucosa subgroup. a: Findings of upper gastrointestinal endoscopy show a reddish small elevated lesion (arrows) of approximately 5 mm in size on the upper position of the gastric cardia. b: Findings of magnifying endoscopy with narrow band imaging show a regular microsurface pattern and an absent microvascular pattern. c: Macroscopic findings of the resected gastric specimen using ESD show a locally elevated lesion (arrows) of 5×5 mm in diameter. d: Histopathological findings of the resected gastric specimen using ESD show a well differentiated tubular adenocarcinoma invading the submucosa (hematoxylin-eosin stain). e: Histopathological findings of the resected gastric specimen using ESD show none atrophic mucosa around early gastric cancer (hematoxylin-eosin stain).
Case 4 of submucosal invasive gastric cancer in the mild atrophic gastric mucosa subgroup. a: Findings of upper gastrointestinal endoscopy show a small depressed lesion (arrows) of approximately 8 mm in size on the upper position of the gastric cardia. b: Findings of upper gastrointestinal endoscopy show a reddish small depressed lesion with occult hemorrhage. c: Macroscopic findings of the resected gastric specimen using ESD show a locally depressed lesion (arrows) of 8×4 mm in diameter. d: Histopathological findings of the resected gastric specimen using ESD show a well-differentiated tubular adenocarcinoma invading the submucosa (hematoxylin-eosin stain).