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Clinicopathological Characteristics and Endoscopic Features of Early Gastric Cancers Diagnosed After *Helicobacter pylori* Eradication

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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 ECGs in the *H. pylori*-EG, it was more likely to be seen in the none to mild atrophic mucosa subgroup compared to the moderate to severe atrophic gastric mucosa subgroup ($P = 0.003$). *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.

1. Introduction

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*-eradiation 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.

2. Materials And Methods

2.1 Study subjects. The study was conducted at Fukuoka University from January 2009 to December 2018. 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 (Figure 1).

2.2. Primary Endpoint. Primary endpoint of this study is to investigate the association between the clinicopathological characteristics and endoscopic features of EGCs diagnosed after *H. pylori* eradication.

2.3. 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 none to 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 (Figure 1).

2.4. 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.

2.5. 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].

2.6. 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 [10]. EGCs were confirmed using histopathological findings of biopsies and ESD samples. The extent and degree of atrophic gastritis was evaluated endoscopically and classified into six categories according to the Kimura and Takemoto classification system (C-1 to O-3) [11].

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

The Medical Ethics Committee of Fukuoka University approved this study (approval number: U20-01-011).

3. Results

3.1. 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* = 0.049). 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 according to Kimura and Takemoto classification system [11] 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.

3.2. 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 none to 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 none to mild atrophic mucosa subgroup and 23 lesions (79%) were in the moderate to severe atrophic mucosa subgroup. Three of 6 none to 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 none to 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 none to mild atrophic mucosa subgroup and only 1 of 23 lesions (4%) in the moderate to severe atrophic mucosa subgroup ($P = 0.003$). Three of 4 submucosal invasive EGC lesions (75%) in none to mild atrophic subgroup had none atrophic mucosa around EGC.

3.3. 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 none to 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 (Figure 2). This result showed that there was no significant association between the duration of EGC incidence and the degree of mucosal atrophy.

3.4. Submucosal invasive early gastric cancer in the H. pylori-EG group. The clinicopathological characteristics and endoscopic features of submucosal invasive five EGCs in the none to 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 (case1, 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 (Figure 3a). NBI-ME revealed a regular microsurface pattern and an absent microvascular pattern (Figure 3b). The tumor was successfully removed en bloc using the ESD method (Figure 3c). The resected specimen was evaluated histopathologically and revealed a well differentiated tubular adenocarcinoma invading into the submucosa (SM1: <50μm) (Figure 3d), none atrophic mucosa around EGC (Figure 3e). In case 4, upper GI endoscopy revealed a reddish small depressed lesion on the upper position of the gastric cardia (Figure 4a, b). The tumor was successfully removed en bloc using the ESD method (Figure 4c). Histopathological examination revealed a well-differentiated tubular adenocarcinoma invading into the submucosa (SM2: 2400μm) and none atrophic mucosa around EGC (Figure 4d).

4. 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 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 0.7–11 years) [3], 4 years (1–15 years) [4], and 3 years (5–15 years) [5]. In this study, the median interval was 3.0 years (1–17 years). In the none to 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. pylor*i eradication regardless of the degree of gastric mucosal atrophy [18].

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.

5. Conclusion

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.

Declarations

Data Availability

Data is available upon request from the authors.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and the Medical Ethics Committee of Fukuoka University approved this study (approval number: U20-01-011).

Conflicts of Interest

The authors have no conflicts of interest to declare.

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Tables

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Figures

Figure 1

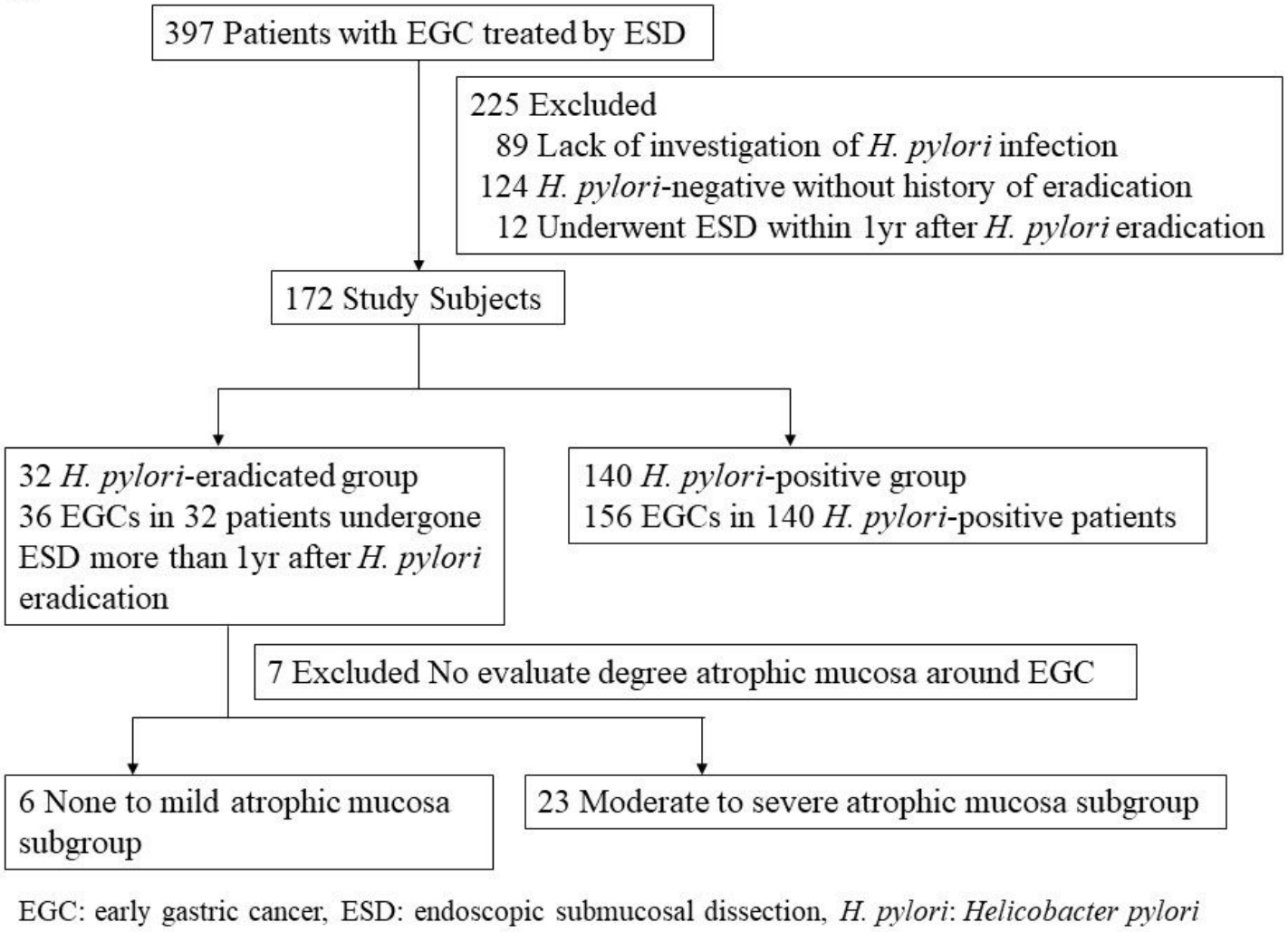
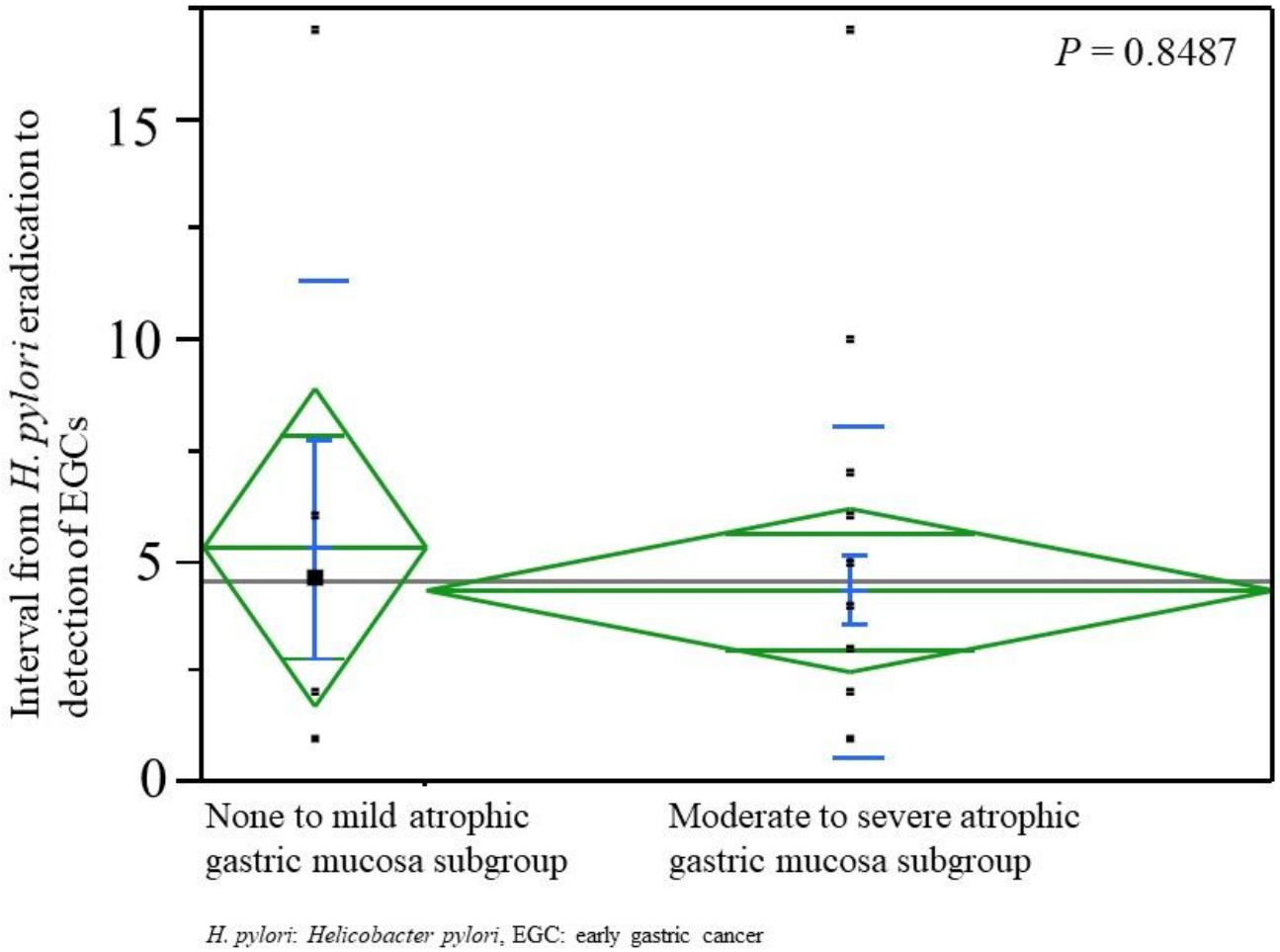


Figure 1

Flow diagram of the study subjects.

Figure 2



H. pylori: *Helicobacter pylori*, EGC: early gastric cancer

Figure 2

Median time interval from eradication of H. pylori to detection of EGC. In the none to mild atrophic gastric mucosa subgroup in the H. pylori-EG, the median interval from eradication therapy to 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.

Figure 3

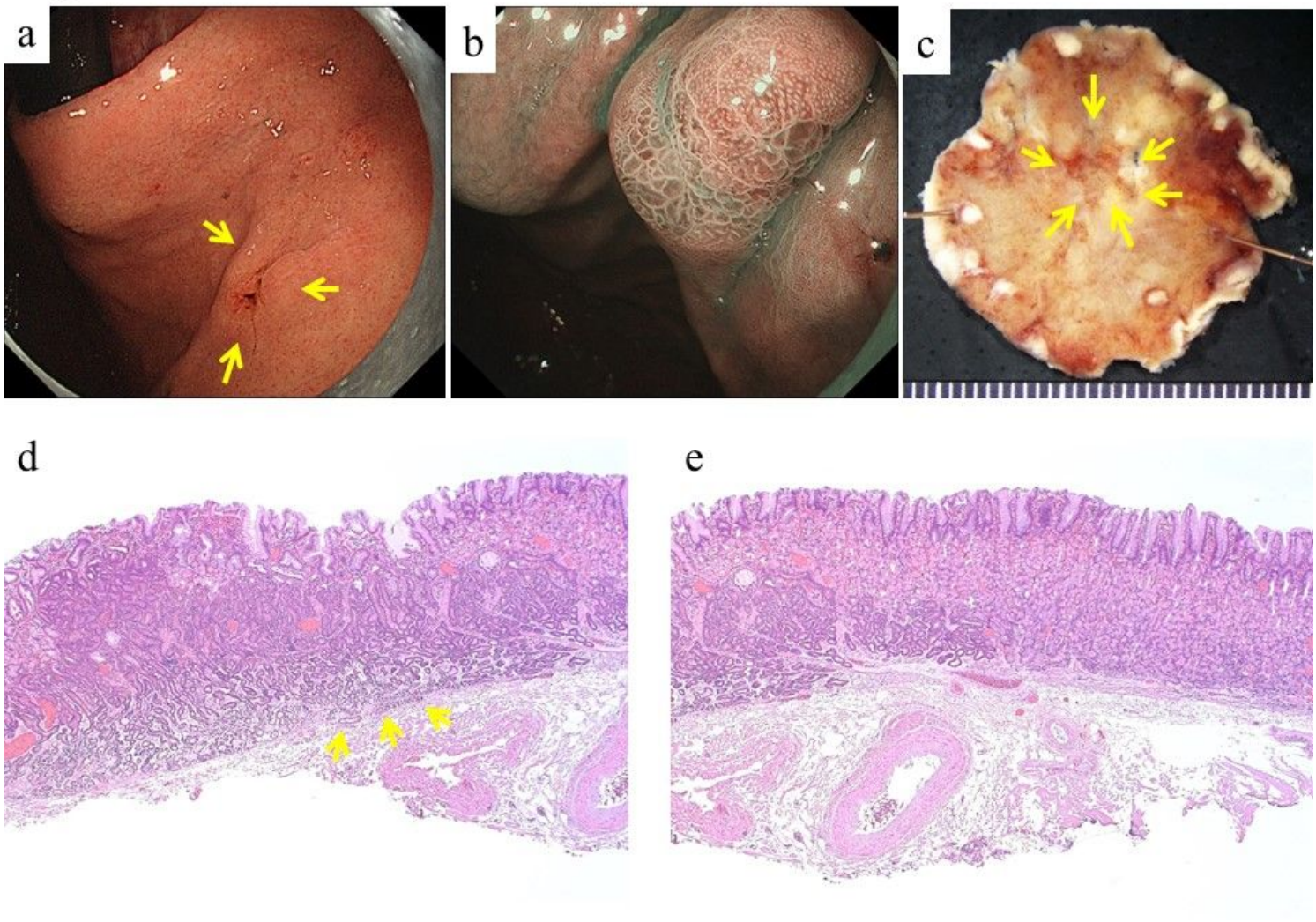


Figure 3

Case 1 of submucosal invasive EGC in the none to mild atrophic gastric mucosa subgroup. a: Findings of upper gastrointestinal endoscopy show a reddish small elevated lesion (arrows) of approximately 5 mm in size in the upper region 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 (SM1: <50μm) (hematoxylin–eosin stain) (arrows). e: Histopathological findings of the resected gastric specimen using ESD show none atrophic mucosa around early gastric cancer (hematoxylin–eosin stain).

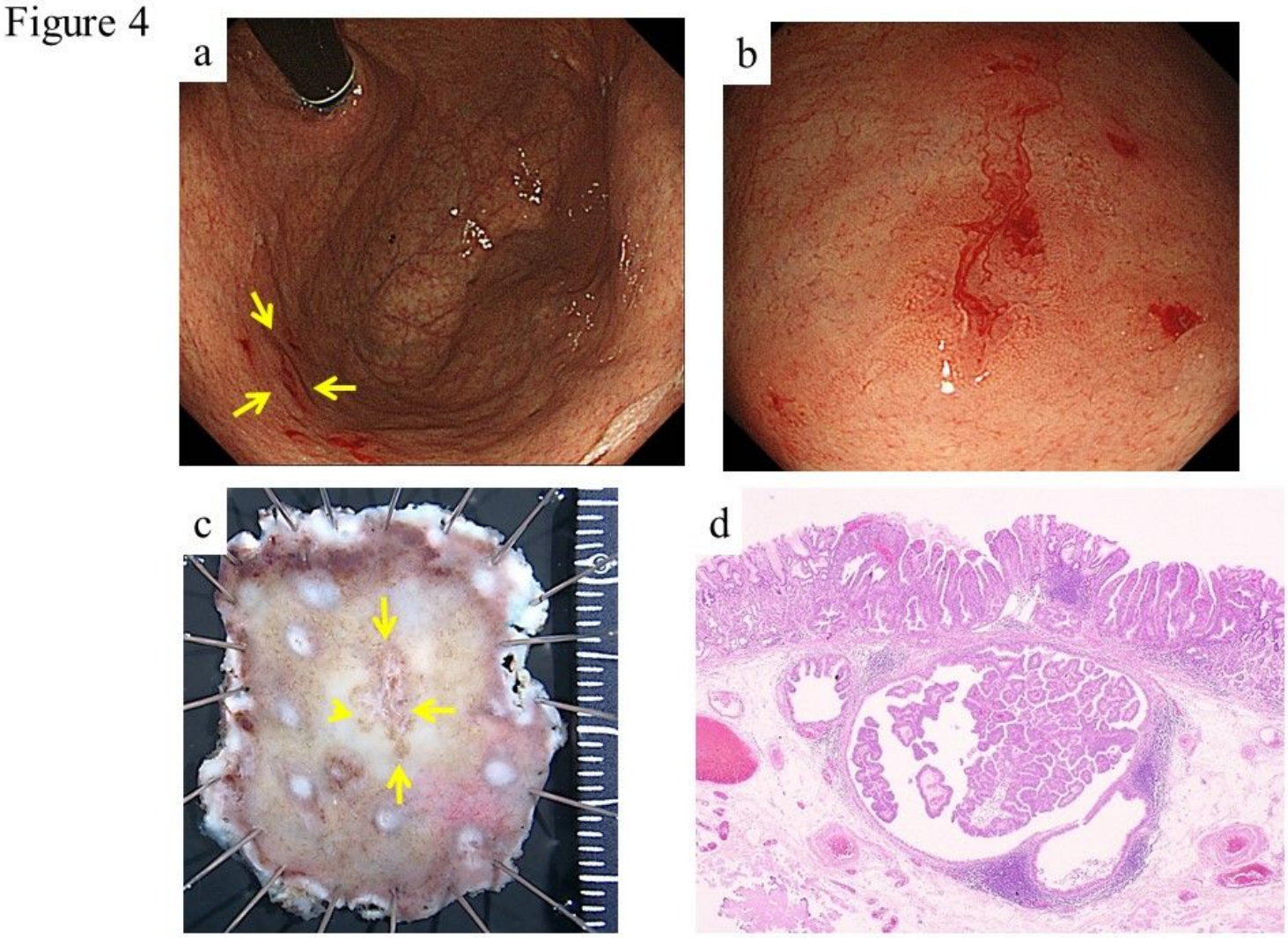


Figure 4

Case 4 of submucosal invasive gastric cancer in the none to mild atrophic gastric mucosa subgroup. a: Findings of upper gastrointestinal endoscopy show a small depressed lesion (arrows) of approximately 8 mm in size in the upper region 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 (SM2: 2400μm) (hematoxylin–eosin stain).

Supplementary Files

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