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Characteristics of Primary and Metachronous Gastric Cancers Discovered after *Helicobacter pylori* Eradication: A Multicenter Propensity Score-Matched Study

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Background/Aims: Gastric cancers develop even after successful *Helicobacter pylori* eradication. We aimed to clarify the characteristics of early gastric cancers discovered after *H. pylori* eradication. **Methods:** A total of 1,053 patients with early gastric cancer treated by endoscopic submucosal dissection were included. After matching the propensity score, we retrospectively investigated the clinicopathological features of 192 patients, including 96 patients who had undergone successful *H. pylori* eradication (*Hp*-eradicated group) and 96 patients who had active *H. pylori* infection (*Hp*-positive group). **Results:** In the *Hp*-eradicated group, early gastric cancers were discovered 1 to 15 years (median, 4.1 years) after *H. pylori* eradication. Compared with *Hp*-positive patients, *Hp*-eradicated patients showed a more frequently depressed configuration (81% vs 53%, respectively, p<0.0001) and a higher trend toward submucosal invasion (18% vs 8%, respectively, p=0.051). A multivariable analysis revealed the macroscopic depressed type to be characteristics of early gastric cancers after *H. pylori* eradication. Among patients in the *Hp*-eradicated group, metachronous cancers showed less frequent depressed lesions (68% vs 84%, respectively, p=0.049) and smaller tumor sizes (median, 11 mm vs 14 mm, respectively, p=0.014) than primary cancers. **Conclusions:** Early gastric cancers after *H. pylori* eradication are characterized by a depressed configuration. Careful follow-up endoscopies are necessary after *H. pylori* eradication. **(Gut Liver 2017;11:628-634)**

Key Words: *Helicobacter pylori* eradication; Early gastric cancer; Endoscopic submucosal dissection; Metachronous gastric cancer; Depressed configuration

INTRODUCTION

Gastric cancer is the fifth most common cancer and the third leading cause of cancer death in the world.[1] It has been clarified that the development of gastric cancer is mostly caused by *Helicobacter pylori* infection.[2-4] In 2008, a Japanese randomized trial showed that *H. pylori* eradication contributed to a significant reduction in the incidence of metachronous gastric cancer (MGC) after endoscopic resection of early primary gastric cancer (PGC).[5] In contrast, our previous retrospective study indicated that *H. pylori* eradication did not significantly reduce the incidence of MGC during a follow-up period of up to 11 years.[6] A meta-analysis of 13 clinical studies from Japan and Korea showed that *H. pylori* eradication after endoscopic resection of early PGC significantly reduced the incidence of MGC.[7-11] However, these studies also have revealed that gastric cancers certainly occur even after successful *H. pylori* eradication. It thus seems to be important to recognize the clinical features of those cancers discovered after *H. pylori* eradication for their appropriate diagnosis and treatment. To date, the characteristics of gastric cancers, which developed after *H. pylori* eradication, have not been clarified.

In the present study, we have conducted a multicenter propensity score-matched study to clarify the characteristics of early gastric cancers discovered after *H. pylori* eradication.

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MATERIALS AND METHODS

1. Study subjects

This was a multicenter, retrospective, and propensity score-matched study from Kyushu University Hospital and other 18 hospitals in Fukuoka, Yamaguchi, and Ehime, Japan. All these hospitals have participated the Kyushu University multicenter endoscopic submucosal dissection database (KYU-MED) study. This database was approved by the Institutional Review Board of Kyushu University Hospital and has been registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) as number UMIN000009190. Written informed consent was obtained from each patient included in the study.

Between June 2003 and October 2014, a total of 2,153 patients with early gastric cancer who were treated by endoscopic submucosal dissection (ESD)[12] at the participating hospitals were registered in KYU-MED study. Of these, 670 patients were not investigated for their *H. pylori* status, and 418 patients showed negative results for examinations for *H. pylori* infection without definite history of *H. pylori* eradication therapy. Of these patients, 58 patients had been assessed by both ^{13}C-urea breath test and IgG serology, 39 by ^{13}C-urea breath test, and two patients by both stool *H. pylori* antigen test and serology, while 251 patients had been tested only by serology, 48 only by rapid urease test, and the remaining 20 patients only by histology. In other 12 patients, gastric cancer was resected within 1 year after *H. pylori* eradication. These 1,100 patients were excluded. The remaining 1,053 patients were further divided into the following two groups: (1) 117 patients who had undergone successful *H. pylori* eradication more than 1 year before, as confirmed by a negative result of ^{13}C-urea breath test or serology at the time of ESD (*Hp*-eradicated group); (2) 936 patients who had an active *H. pylori* infection, as determined by the rapid urease test, ^{13}C-urea breath test, stool *H. pylori* antigen test, histology or serology (*Hp*-positive group). After analyzing the baseline clinical characteristics of 1,053 patients, 1:1 propensity score-matching was performed to minimize any selection bias.[13] Finally, a total of 192 matched patients, with 96 patients in each group, were included in the analysis (Fig. 1).

2. Clinicopathological assessment of gastric cancers

In this study, PGC was defined as a gastric carcinoma that developed in a patient who had no previous history of gastric cancer. MGC was defined as a new carcinoma that developed in other areas at least 1 year after the endoscopic resection of the initial gastric cancer. In patients with MGC, the initial early gastric cancer had been treated by ESD or endoscopic mucosal resection in another hospital. All endoscopic examinations and ESDs were performed by the specialized endoscopists who had a license for Board Certification of Japan Gastroenterological Endoscopy Society in 18 participated hospitals.

The histopathological assessment of the resected specimens was performed by the senior pathologist in each hospital. In 44 patients who had more than one carcinoma at the time of ESD, we evaluated only one carcinoma of which the depth of invasion and/or size was greater than the others. Among these 44 patients, we chose the carcinoma invading the submucosa in spite of the smaller size in three patients. Location, macroscopic type, and histological findings of gastric cancers were classified according to the Japanese classification and Paris classification of gastric carcinoma.[14,15] Namely, the location was classified by dividing stomach into three equal sections: upper, middle, and lower. Macroscopic type was classified either as elevated (type 0–I, IIa, and IIa+IIc) or as depressed type (type 0–IIb, IIc, IIc+IIa, IIc+III, and III). Histopathologically, well and/or moderately differentiated adenocarcinomas were regarded as differentiated type, while poorly differentiated adenocarcinoma and/or signet-

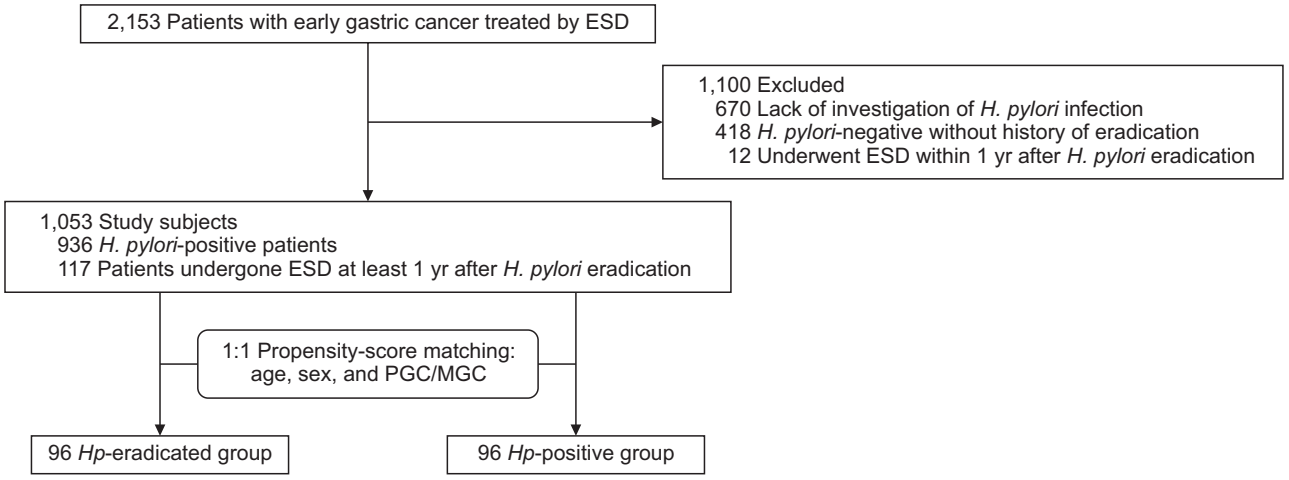

Fig. 1. Flow of the study subjects.
ESD, endoscopic submucosal dissection; PGC, primary gastric cancer; MGC, metachronous gastric cancer; *Hp*, *Helicobacter pylori*.

ring cell carcinoma were as undifferentiated type. Presence or absence of ulcerations with or without scars, submucosal invasion, lymphatic invasion and venous invasion were also assessed with the resected specimens. When massive invasion to the submucosa and/or lymphovascular invasion by carcinoma was observed, an additional gastrectomy with regional lymph node dissection was recommended to the patient.

3. Statistical analysis

Two of the authors (Y.M. and F.I.) performed all the statistical analyses. F.I. is an expert for the statistics. We used propensity score-matching analysis to adjust significant differences in the baseline clinical characteristics of patients and to reduce the influence of possible confounding factors. Propensity scores were calculated using a logistic regression model and variables included in the model were age, sex, and PGC/MGC (Fig. 1). After propensity scores were estimated, one-to-one nearest-neighbor matching without replacement was performed with a caliper of width equal to 0.2 of the standard deviation of the logit of the propensity score.[13] Before and after propensity score-matching, we compared the clinicopathological characteristics of these enrolled patients between *Hp*-positive group and *Hp*-eradicated group. Among *Hp*-eradicated patients, the clinicopathological characteristics were also compared between PGC and MGC. The parametric data were expressed as the medians (range). The numerical data were compared using the Mann-Whitney U test, and the categorical data were compared by the Fisher exact probability test or the chi-square test. In order to identify the independent characteristics of early gastric cancer after *H. pylori* eradication, the variables that were assumed to influence the characteristics of early gastric cancer with p-values less than 0.2 were put into a multivariable analysis using logistic regression

Table 1. Comparison of Clinicopathological Characteristics between *Hp*-Eradicated and *Hp*-Positive Groups before and after Propensity-Score Matching

Characteristic	All patients (n=1,053)			Propensity-matched patients (n=192)		
	Hp-eradicated (n=117)	*Hp*-positive (n=936)	p-value	*Hp*-eradicated (n=96)	*Hp*-positive (n=96)	p-value
Sex			0.075			0.855
Male	95 (81)	691 (74)		77 (80)	78 (81)	
Female	22 (19)	245 (26)		19 (20)	18 (19)	
Age, yr	71 (46–90)	71 (30–96)	0.397	72 (46–90)	72 (47–92)	0.886
Primary or metachronous cancers			<0.0001			1.000
Primary gastric cancer	67 (57)	907 (97)		67 (70)	67 (70)	
Metachronous gastric cancer	50 (43)	29 (3)		29 (30)	29 (30)	
Location			0.358			0.982
Upper	24 (21)	148 (16)		21 (22)	22 (23)	
Middle	45 (38)	352 (38)		36 (37)	35 (36)	
Lower	48 (41)	436 (46)		39 (41)	39 (41)	
Macroscopic type			0.001			<0.0001
Elevated type	27 (23)	354 (38)		18 (19)	45 (47)	
Depressed type	90 (77)	582 (62)		78 (81)	51 (53)	
Size (diameter), mm	13 (2–75)	14 (1–100)	0.052	13 (2–75)	14 (2–60)	0.820
Histology			0.473			0.721
Differentiated type	114 (97)	892 (95)		93 (97)	91 (95)	
Undifferentiated type	3 (3)	44 (5)		3 (3)	5 (5)	
Depth of invasion			0.190			0.051
Mucosa	97 (83)	818 (87)		79 (82)	88 (92)	
Submucosa	20 (17)	118 (13)		17 (18)	8 (8)	
Ulceration or scar	11 (9.4)	66 (7.1)	0.374	9 (9.4)	7 (7.3)	0.601
Lymphatic invasion	7 (6.0)	25 (2.7)	0.076	6 (6.3)	3 (3.1)	0.497
Venous invasion	2 (1.7)	12 (1.3)	0.663	1 (1)	0	1.000
Adjunctive gastrectomy after ESD	11 (9.4)	66 (7.1)	0.374	10 (10)	5 (5.2)	0.175

Data are presented as number (%) or median (range).
Hp, *Helicobacter pylori*; ESD, endoscopic submucosal dissection.

model. A p-value of <0.05 was considered to be statistically significant for each test. All analyses were performed with the JMP Pro 12.2.0 software (SAS Institute, Cary, NC, USA).

RESULTS

1. Comparison between *Hp*-eradicated group and *Hp*-positive group

In *Hp*-eradicated patients, early gastric cancers were discovered 1 to 15 years (median, 4.1 years) after *H. pylori* eradication. Table 1 compares the clinicopathological features of patients between *Hp*-eradicated group and *Hp*-positive group before and after propensity score-matching. Before propensity score-matching, male patients were tended to be more frequent in *Hp*-eradicated group (81%) than in *Hp*-positive group (74%; p=0.075). MGC was more frequent in *Hp*-eradicated group (50/117 patients, 43%) than in *Hp*-positive group (29/936 patients, 3%; p<0.0001). Depressed configuration was more frequent in *Hp*-eradicated group (77%) than in *Hp*-positive group (62%; p=0.001). There were trends towards smaller size of cancer (median, 13 mm vs 14 mm; p=0.052) and high prevalence of lymphatic invasion (6% vs 2.7%; p=0.076) in *Hp*-eradicated group than in *Hp*-positive group.

After propensity score-matching, 67 patients with PGC and 29 patients with MGC were included in each group (p=1.000). Macroscopically, depressed type was more frequent in *Hp*-erad-

Table 2. Results of a Multivariate Logistic Regression Analysis for the Characteristics of Early Gastric Cancers Discovered after *Helicobacter pylori* Eradication in Propensity-Matched Patients

	OR	95% CI	p-value
Macroscopic type			
Depressed type vs elevated type	3.80	2.00–7.49	<0.0001
Depth of invasion			
Submucosa vs mucosa	1.85	0.65–5.69	0.252
Adjunctive gastrectomy after ESD			
Necessary vs unnecessary	1.56	0.40–6.43	0.518

OR, odds ratio; CI, confidence interval; ESD, endoscopic submucosal dissection.

Table 3. Comparison of the Clinicopathological Characteristics among All Patients with PGC and Those with MGC Discovered after *Helicobacter pylori* Eradication

	PGC (n=67)	MGC (n=50)	p-value
Sex			0.847
Male	54 (81)	41 (82)	
Female	13 (19)	9 (18)	
Age, yr	69 (46–85)	74 (56–90)	0.003
Time after *H. pylori* eradication, yr	4.9 (1.0–15.0)	3.8 (1.0–14.0)	0.263
Time after latest negative endoscopy, yr	1.9 (0.5–10.0)	1.0 (0.5–2.0)	<0.0001
Location			0.627
Upper	15 (23)	9 (18)	
Middle	27 (40)	18 (36)	
Lower	25 (37)	23 (46)	
Macroscopic type			0.049
Elevated type	11 (16)	16 (32)	
Depressed type	56 (84)	34 (68)	
Size (diameter), mm	14 (3–75)	11 (2–43)	0.014
Histology			1.000
Differentiated type	65 (97)	49 (98)	
Undifferentiated type	2 (3)	1 (2)	
Depth of invasion			0.473
Mucosa	57 (85)	40 (80)	
Submucosa	10 (15)	10 (20)	
Ulceration or scar	5 (7.5)	6 (12)	0.408
Lymphatic invasion	2 (3)	5 (10)	0.136
Venous invasion	0	2 (4)	0.281
Adjunctive gastrectomy after ESD	4 (6)	7 (14)	0.201

Data are presented as number (%) or median (range).
PGC, primary gastric cancer; MGC, metachronous gastric cancer; ESD, endoscopic submucosal dissection.

icated group (81%) than in *Hp*-positive group (53%; p<0.0001). Submucosal invasion of carcinoma tended to be more frequent in *Hp*-eradicated group (18%) than in *Hp*-positive group (8%; p=0.051). Other factors, including sex, age, location, size, histologic type, ulceration, lymphatic and venous invasion, and adjunctive gastrectomy after ESD, did not differ between two groups.

2. Independent clinicopathological characteristics of early gastric cancer after *H. pylori* eradication

As shown in Table 2, our multivariable logistic regression analysis determined that macroscopic depressed type (odds ratio, 3.80; 95% confidence interval, 2.00 to 7.49; p<0.0001) was the sole independent characteristics of early gastric cancer after *H. pylori* eradication in propensity-matched patients. Other factors, including depth of invasion and adjunctive gastrectomy after ESD, did not significantly associate with cases discovered after *H. pylori* eradication.

3. Comparison between PGC and MGC discovered after *H. pylori* eradication

Table 3 compares the clinicopathological features between patients with PGC and those with MGC in *Hp*-eradicated group before propensity score-matching. Patients with MGC were older than those with PGC (median, 74 years vs 69 years; p=0.003). The median time interval between *H. pylori* eradication and ESD of cancers did not differ between patients with PGC (4.9 years) and those with MGC (3.8 years). By contrast, time interval between the latest negative endoscopy and ESD of cancers was longer in patients with PGC than in those with MGC (median, 1.9 years vs 1.0 years; p<0.0001). Macroscopically, depressed lesion was more frequent in PGC (84%) than in MGC (68%; p=0.049). The size of MGC was smaller than that of PGC (median, 11 mm vs 14 mm; p=0.014). There were trends towards high prevalence of lymphatic invasion (10% vs 3%), venous invasion (4% vs 0%), and adjunctive gastrectomy (14% vs 6%) in MGC than in PGC. However, these differences were not statistical significant. Other factors, including sex, location, and histologic type did not differ between two groups.

DISCUSSION

In the present study, we confirmed that gastric cancers including both PGCs and MGCs developed during a long-term period of up to 15 years (median, 4 years) after *H. pylori* eradiation. Compared to *H. pylori*-positive cancers, early gastric cancer after *H. pylori* eradication had more frequent depressed configuration and a higher trend of submucosal invasion. Our multivariable analysis revealed macroscopic depressed type to be independent characteristics of early gastric cancer after *H. pylori* eradication.

To date, there have been reported several studies investigating the characteristics of gastric cancers discovered after *H. pylori* eradication.[16-20] In a follow-up study, Kamada *et al*.[16] found that gastric cancers discovered after *H. pylori* eradication were characterized by noncardiac location, small size ≤20 mm, macroscopically ulcerative type, and histologic intestinal type. In a pathological study by Yamamoto *et al*.,[19] gastric cancers detected after *H. pylori* eradication showed smaller size, more frequent macroscopic depressed type, and lower Ki-67 labeling index than *H. pylori*-positive gastric cancers. They speculated that improvement of gastric acid secretion induced after *H. pylori* eradication may prevent the elevated growth in the surface of gastric cancers.[19] Interestingly, Ito *et al*.[21] indicated that about half of the elevated type of gastric carcinoma and adenoma became flattened only one month after *H. pylori* eradication. They speculated that *H. pylori* eradication might have directly inhibited the upward (expansive) growth of the gastric tumor. It should be noted that the number of subjects with gastric cancers discovered after the eradication in our current study (n=96) was much larger than in these previous studies (n=18 to 47).[16-20] In addition, this was a propensity score-matched study. We thus consider our results to possess higher reliability than those of previous studies.

In the present study, MGC was more frequent in *Hp*-eradicated group (43%) than in *Hp*-positive group (3%) before propensity score-matching. Since the publication of Japanese randomized trial in 2008,[5] almost all patients with first early gastric cancer treated by endoscopic resection in Japan have undergone *H. pylori* eradication therapy.[22,23] Thus, absolute numbers of *H. pylori*-positive patients with MGC seem to have decreased in these recent years. It has been demonstrated that severe mucosal atrophy with high risk of subsequent development of MGCs still remains in most of those patients with a history of removal of early gastric cancer, even after successful eradication of *H. pylori*.[6,24] Therefore, careful follow-up endoscopy should be applied especially in patients with early gastric cancer treated by endoscopic resection and *H. pylori* eradication.

It has been considered that *H. pylori* eradication may inhibit the progression of gastric cancer to some extent.[19,25] A Korean randomized trial showed that all the 10 MGCs in eradicated group were confined to the mucosa, while six of 14 (43%) MGCs in *H. pylori*-positive group invaded submucosa or muscularis propria.[8] In our present matched study, however, submucosal invasion of carcinoma tended to be more frequent in *Hp*-eradicated group (18%) than in *Hp*-positive group (8%; p=0.051). In a Japanese randomized trial, the prevalence of submucosal invasion in MGCs did not differ between *Hp*-eradicated group (11%) and *H. pylori*-positive group (4%).[5] It thus seems controversial as to whether invasive MGCs increase or decrease after *H. pylori* eradication. Several studies have revealed that normal columnar epithelia and "gastritis-like" appearances are often observed on the surface of early gastric cancers after *H. pylori* eradication.[21,26] We thus speculate that such cancers tend

to show indistinct endoscopic appearances and to take longer time to be discovered in some cases, and as a consequence, they invade the submucosa during the prolonged period.

In *Hp*-eradicated group, tumor size was larger depressed lesion was more frequent in PGC than in MGC (Table 3). This observation was probably associated with the fact that time after latest negative endoscopy was longer in patients with PGC (1.9 years) than in those with MGC (1.0 years). However, higher trends of lymphatic invasion, venous invasion, and adjunctive gastrectomy in MGC than in PGC seem to suggest that MGC after *H. pylori* eradication may haven more aggressive behavior.

Our present study has several limitations. First, our study subjects were limited to patients with early gastric cancer treated by ESD, and patients with advanced gastric cancers or those obviously invading the submucosa were excluded. Thus, our results might not represent the characteristics of all the gastric cancers discovered after *H. pylori* eradication. Second, many subjects were excluded because of lack of investigation for *H. pylori* infection (n=670) or negative results for *H. pylori* (n=418). Among *H. pylori*-negative patients (n=418), 319 patients were examined only by the rapid urease test, histology, or serology. Therefore, false-negative patients who were not confirmed by ^{13}C-urea breath test or stool *H. pylori* antigen test would be included in these patients. Third, we had no data of background mucosal atrophy in each patient and we obtained the data of latest negative endoscopy only for *Hp*-eradicated group. In addition, retrospective nature of the study might have introduced certain selection biases.

In conclusion, our multicenter propensity score-matched study revealed that early gastric cancers after *H. pylori* eradication are characterized by depressed configuration and higher trend of submucosal invasion. The long-term risk for the development of gastric cancer exists even in patients who have achieved successful *H. pylori* eradication. We should perform follow-up endoscopy carefully after *H. pylori* eradication, with special attentions to depressed type gastric cancer. Further investigations of larger number of patients with much longer follow-up periods are therefore still required to clarify the clinicopathological characteristics of gastric cancers that develop after *H. pylori* eradication.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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