Original Article

Characteristics of gastric cancer detected within 1 year after successful eradication of *Helicobacter pylori*

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Gastric cancers are sometimes diagnosed in patients who have successfully undergone *Helicobacter pylori* (*H. pylori*) eradication. We analyzed the clinicopathological features of gastric cancers detected after eradication to clarify their characteristics. We reviewed 31 patients with 34 cases of gastric cancer detected after successful *H. pylori* eradication. Clinicopathological characteristics analyzed included interval since eradication, interval since last endoscopy, tumor size, and depth of invasion. Patients were classified into two groups: early detection (<1 year since eradication) and delayed detection (≥1 year since eradication). The interval since last endoscopy was significantly shorter in the early detection group than in the delayed detection group. However, gastric cancers were significantly larger and more invasive in the early detection group than in the delayed detection group. In conclusion, diligent endoscopy is necessary during the first year after successful *H. pylori* eradication. (The University Hospital Medical Information Network clinical trial registration number is UMIN000018541.)

***Key Words*: gastric cancer, *H. pylori*, eradication**

Gastric cancer is a major cause of cancer-related death worldwide.[1,2] The association between *Helicobacter pylori* (*H. pylori*) infection and the development of gastric cancer is well established.[3–5] Although *H. pylori* eradication is considered preventative against the development of gastric cancer, tumors have sometimes been discovered after successful bacterial eradication.[6,7] Gastric cancers detected after eradication are typically reported to be small and to have a lower cell proliferation rate.[8,9] Many studies have evaluated gastric cancers that were detected at least 1 year after *H. pylori* eradication.[9–11] Therefore, there is a lack of knowledge and understanding about gastric cancers detected within 1 year after eradication. Hence, we analyzed the clinicopathological features of gastric cancers detected within a year of *H. pylori* eradication in order to clarify their characteristics.

Methods

Subjects. For the purposes of this study, we defined gastric cancer after successful *H. pylori* eradication as gastric cancer that was diagnosed after eradication but had not been detected before the eradication. Data for 112 gastric cancers in 96 consecutive patients were retrospectively reviewed. The patients were diagnosed via endoscopic examination in the Toyoshima Endoscopy Clinic between 2008 and 2013. Patients with the following criteria were excluded: (1) *H. pylori*-negative patients without a history of eradication therapy; (2) *H. pylori*-positive patients without a history of eradication therapy; (3) *H. pylori*-positive patients with a history of unsuccessful eradication; (4) patients with an unclear *H. pylori* infection status; (5) patients with a history of gastrectomy; and (6) patients who did not undergo upper gastrointestinal endoscopy before the eradication. Ultimately, 34 gastric cancers in 31 patients met our criteria for successful *H. pylori* eradication.

***H. pylori* infection status.** *H. pylori* infection status was assessed using a ^{13}C-urea breath test, stool antigen analysis, or *H. pylori*-specific immunoglobulin G antibodies in the serum.[12,13] When patients had no history of eradication therapy, *H. pylori* infection was confirmed when any one of these tests was positive. After eradication therapy, cured status was confirmed via a ^{13}C-urea breath test.[14]

Clinicopathological assessment. Clinicopathological findings, including the interval since eradication, interval since last endoscopy, age, sex, mucosal atrophy, tumor size, depth of invasion, cancer stage, location, macroscopic type, and histological type, were reviewed. The interval since eradication was defined as the interval between the eradication treatment and the detection of gastric cancer. The interval since last endoscopy was defined as the interval between the endoscopy wherein gastric cancer was detected and the previous endoscopy. Kimura and Takemoto[15] divided gastric mucosal atrophy into 6 grades (C-I, C-II, C-III, O-I, O-II, and O-III) based on endoscopic findings. The atrophic border is the boundary between the pyloric and fundic gland regions, which can be recognized endoscopically based on the difference in color and height of the gastric mucosa on either side of the border. It has been demonstrated that mucosal atrophy progresses sequentially from C-I to O-III; this endoscopic classification is consistent with the updated Sydney System for the classification of gastric atrophy.[16] If the border of the gastric atrophy was only on the lesser curvature of the stomach, it was defined as the closed type (C-I, C-II, C-III). If the border was orally shifted and was not limited to the lesser curvature, it was defined as the open type (O-I, O-II, and O-III). Tumor size was expressed as the longest diameter measured on a resected specimen. The depth of tumor invasion was divided into four categories: M (tumor confined to mucosa), SM (submucosal

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invasion), MP (muscularis propria invasion), and SS (serosal invasion). Early gastric carcinoma was defined as invasive carcinoma confined to the mucosa and/or submucosa. Advanced gastric cancer was defined as gastric cancer that invades deeper than the submucosa.[17] Tumors were classified according to the Lauren classification system as intestinal- or diffuse-type tumors.[18]

Statistical analysis. The patients were classified into an early detection group (interval since eradication <1 year) and a delayed detection group (interval since eradication ≥1 year). Differences between the groups were compared using the Student's *t* test and/or Welch's *t* test for continuous variables, and Fisher's exact test or the cumulative chi-squared test for categorical variables. A *p* value of less than 0.05 was considered statistically significant. The data were analyzed using the Stat Mate IV software (ATOMS, Tokyo, Japan).

Ethics. The study was conducted with the approval of the Ethics Committee of external organization, and informed consent was obtained from all patients. The University Hospital Medical Information Network clinical trial registration number is UMIN000018541.

Results

A flowchart of gastric tumors is shown in Fig. 1. Among the 112 tumors detected in 96 patients, 78 were excluded from the present study. Three gastric cancers in 3 *H. pylori*-negative patients and 59 gastric cancers in 46 *H. pylori*-positive patients without eradication histories were excluded. Five gastric cancers in 5 *H. pylori*-positive patients with unsuccessful eradication histories were also excluded. Also excluded were 9 cases of gastric cancer in 9 patients with an *H. pylori* infection status, 1 case of gastric cancer in a patient with a subtotal gastrectomy history, and 1 case of gastric cancer in a patient who did not undergo endoscopy before the eradication. Ultimately, 34 gastric cancers that occurred after successful *H. pylori* eradication in 31 patients were evaluated for this study.

Table 1 shows the characteristics of the 34 tumors included in the present study. Eight tumors in 8 patients were classified into the early detection group, while 26 tumors in 23 patients were categorized into the delayed detection group. The mean intervals since last endoscopy in the early and delayed detection groups were 7 ± 2.9 and 14.2 ± 11.8 months (mean ± SD), respectively.

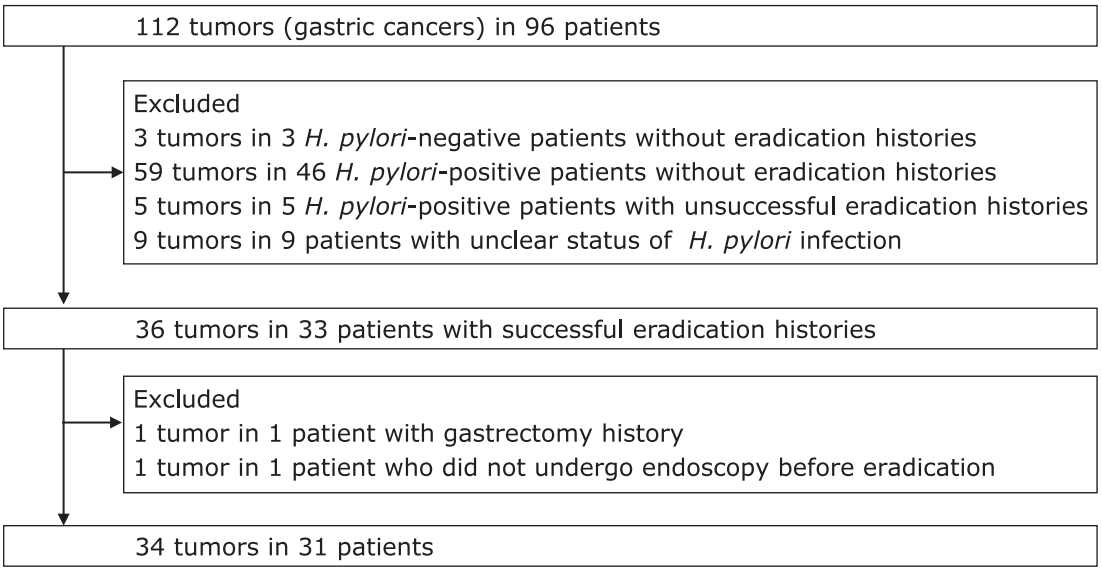

Fig. 1. Flow chart of the gastric tumors analyzed in this study. A total of 112 gastric cancers in 96 consecutive patients were reviewed. After exclusion criteria were applied, 34 gastric cancers detected after successful *H. pylori* eradication in 31 patients were further evaluated.

Table 1. Characteristics of 34 tumors in 31 patients included in the present study

Characteristics	All *n* = 34	Interval from eradication <1 year *n* = 8	Interval from eradication ≥1 year *n* = 26	*p* value
Interval from eradication (months)	41 ± 30.1*	5.1 ± 3.1*	52 ± 25.7*	<0.001
Interval of endoscopy (months)	12.5 ± 10.8*	7 ± 2.9*	14.2 ± 11.8*	0.008
Age	65.7 ± 12.4*	64.4 ± 14.9*	66.1 ± 11.9*	0.898
Sex (male)	19 (55.9%)	5 (62.5%)	14 (53.8%)	0.98
Atrophy (close/open)	5/29	0/8	5/21	0.44
Location (upper/middle/lower)	5/15/14	1/4/3	4/11/11	0.766
Size (mm)	14.4 ± 14.1*	23 ± 16.9*	11.8 ± 12.3*	0.047
Macroscopic type (elevated/flat/depressed)	9/2/23	4/0/4	5/2/19	0.11
Histological type (intestinal/diffuse)	29/5	6/2	23/3	0.712
Depth (M/SM/MP/SS)	28/4/1/1	4/2/1/1	24/2/0/0	<0.001
Cancer stage (early/advanced)	32/2	6/2	26/0	<0.05

*Mean ± SD. M, tumor confined mucosa; SM, submucosal invasion; MP, muscularis propria invasion; SS, serosal invasion.

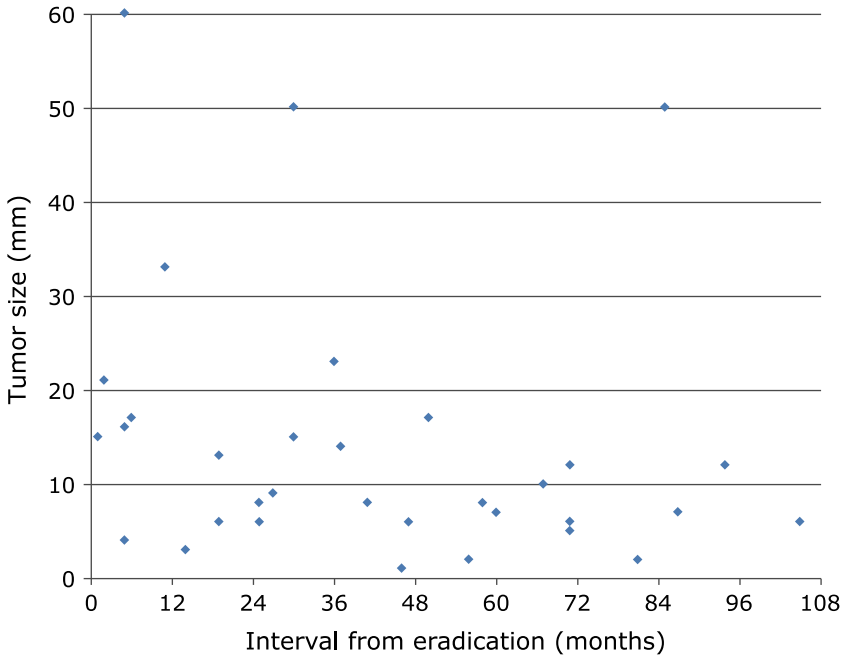

Fig. 2. Scatter plot in between interval from eradication interval and tumor size. The median tumor sizes in the early and delayed detection groups were 17.5 and 8 mm, respectively.

The interval since last endoscopy in the early detection group was significantly shorter than that in the delayed detection group ($p = 0.008$). There were no significant differences between the groups in terms of patient age, sex, and mucosal atrophy. The mean tumor sizes in the early and delayed detection groups were 23 ± 16.9 and 11.8 ± 12.3 mm, respectively (Fig. 2). The mean tumor size in the early detection group was significantly larger than that in the delayed detection group ($p = 0.047$). Advanced cancer was more frequently observed in the early detection group ($p<0.05$), and tumor invasion was deeper in the early detection group than in the delayed detection group. There were no significant differences between the groups in terms of other clinicopathological findings. Fig. 3 and 4 show representative endoscopic images.

Discussion

In this study, we found that gastric cancers detected within 1 year after *H. pylori* eradication were more invasive than those detected more than 1 year after eradication, despite more frequent endoscopic follow-up evaluations in the former group.

Eradication of *H. pylori* results in the healing of some gastrointestinal diseases, such as chronic active gastritis, peptic ulcer diseases, gastric hyperplastic polyp, and gastric mucosa-associated lymphoid tissue lymphoma.[19,20] A recent study on the morphologic changes in gastric adenomas after *H. pylori* eradication revealed that 12 lesions (44%) showed macroscopic and histologic regression at an average of 19.9 months after eradication.[21] A meta-analysis of six randomized controlled trials confirmed that successful eradication reduced the risk of gastric cancer (relative risk 0.66; 95% confidence interval: 0.46–0.95).[6] Take *et al.*[22] reported that the rate of developing gastric cancer after eradication was 0.3% per year, and that the cancer could develop as long as 10 years after *H. pylori* eradication, indicating that careful endoscopic examination is necessary even after successful eradication.

Gastric cancer generally has a long natural course, with a relatively long doubling time of 1.4 years.[23] Most gastric cancers found within 1 year after eradication may have been missed on previous endoscopic screenings.[24] It is well known that *H. pylori* infection causes endoscopic gastritis, which presents as erythema, erosion, hemorrhage, and large gastric folds.[16] *H. pylori* eradication improves gastritis as determined endoscopically and histologically.[25,26] Kato *et al.*[27] also reported that grading of endoscopic findings, including diffuse redness, spotty redness, non-transparency of gastric juice, and enlarged folds, was lower in their successful eradication group than in their unsuccessful eradication group. Improvement in endoscopic gastritis with *H. pylori* eradication may contribute to the detection of gastric cancer within 1 year after eradication. Thus, early endoscopic examination after successful eradication is important for detecting gastric cancer.

Yamamoto *et al.*[8] compared the clinicopathological findings between gastric cancers detected after successful eradication and gastric cancers that occur during *H. pylori* infection. They reported that the mean diameter of gastric cancer was smaller, and the Ki-67 index was lower, in the eradication group than in the infection group. Matsuo *et al.*[9] also reported that Wnt5a expression was significantly lower in the eradication group than in the infection group. These data indicate that *H. pylori* might have a direct effect on the proliferation dynamics of cancer cells, and that the proliferative capability might be suppressed by *H. pylori* eradication. In our study, most of the gastric cancers detected within 1 year after successful eradication had already developed prior to the eradication; therefore, the characteristics of gastric cancer detected within 1 year after successful eradication could be similar to those of gastric cancers detected during *H. pylori* infection.

Periodic endoscopic follow-up, even after *H. pylori* eradication, is important for detecting early gastric cancer.[28] Asaka *et al.*[29,30] proposed an endoscopic follow-up schedule after eradication. In patients with atrophic gastritis, endoscopic follow-up after 1 year is recommended.[29] Our data also support the recommendation of endoscopic follow-up after 1 year.

This study contains several limitations. First, it was difficult to distinguish between missed lesions and new lesions. Second, this study was retrospective in nature, and a follow-up study should be

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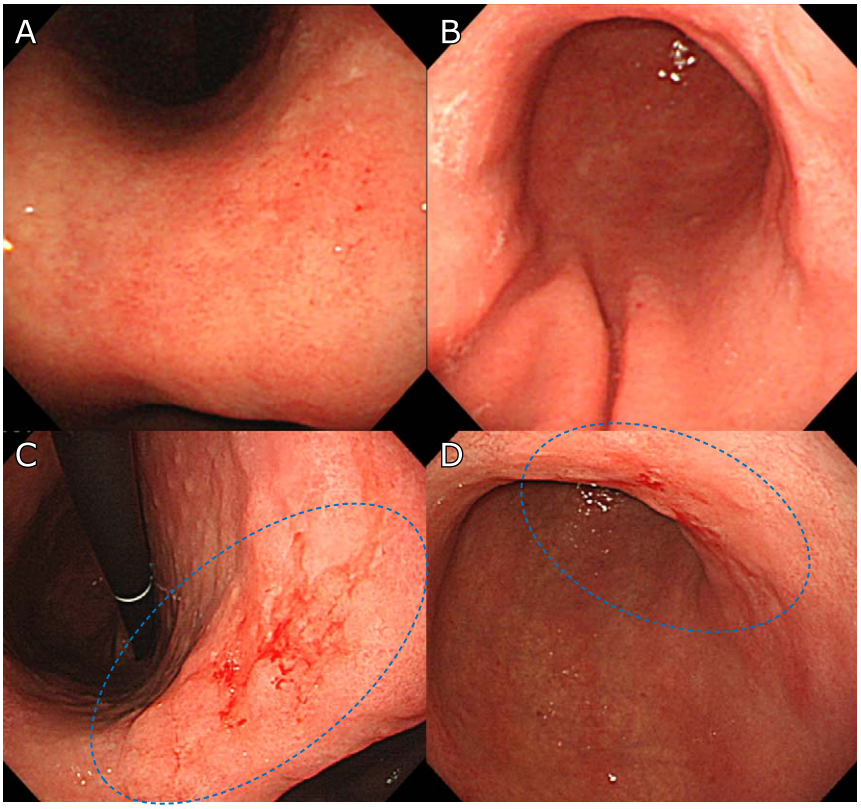

Fig. 3. Representative endoscopic images before and after eradication. (A, B) Before eradication, gastric cancer was not detected. (C, D) After eradication (11 months), gastric cancer was detected. The size was 33 mm, the depth of tumor invasion was muscularis propria, and the histology subtype was moderately-differentiated adenocarcinoma.

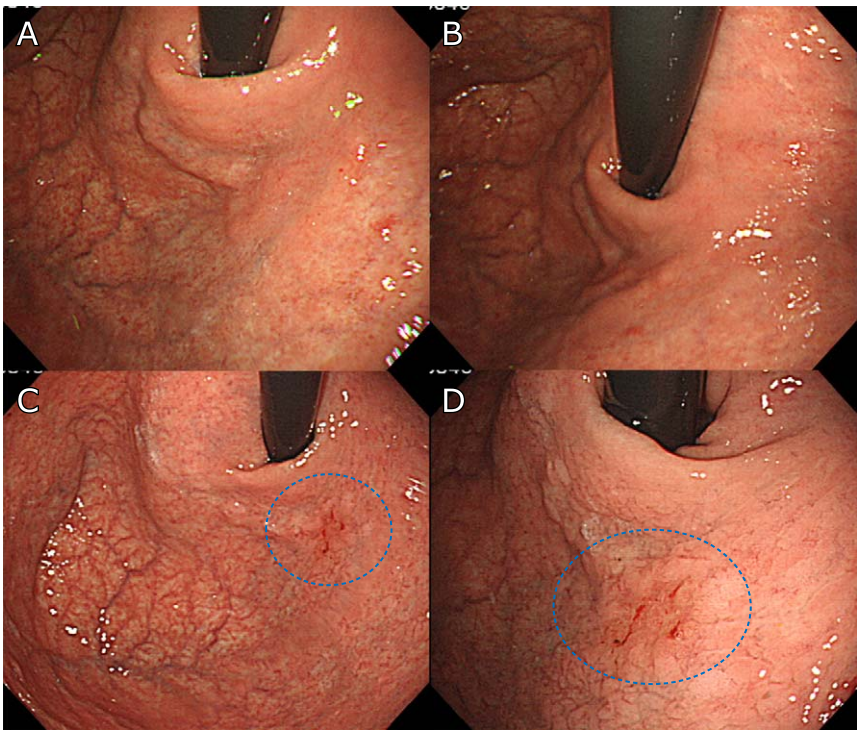

Fig. 4. Representative endoscopic images before and after eradication. (A, B) Before eradication, gastric cancer was not detected. (C, D) After eradication (19 months), gastric cancer was detected. The size was 13 mm, the depth of tumor invasion was mucosa, and the histology subtype was well-differentiated adenocarcinoma.

performed prospectively to confirm the characteristics of gastric cancer detected within 1 year after successful eradication.

In conclusion, we found that gastric cancers detected within 1 year of *H. pylori* eradication were larger and more invasive than those detected 1 year or more after eradication, despite more frequent endoscopic follow-up evaluations. Thus, an endoscopic follow-up strategy after *H. pylori* eradication should include diligent endoscopy evaluation during the 1st year.

Conflict of Interest

No potential conflicts of interest were disclosed.

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