ORIGINAL ARTICLE

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Dynamic Changes in *Helicobacter pylori* Status Following Gastric Cancer Surgery

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Background/Aims: *Helicobacter pylori* eradication is recommended in patients with early gastric cancer. However, the possibility of spontaneous regression raises a question for clinicians about the need for "retesting" postoperative *H. pylori* status. **Methods:** Patients who underwent curative gastrectomy at Seoul National University Bundang Hospital and had a positive *H. pylori* status without eradication therapy at the time of gastric cancer diagnosis were prospectively enrolled in this study. *H. pylori* status and atrophic gastritis (AG) and intestinal metaplasia (IM) histologic status were assessed pre- and postoperatively. **Results:** One hundred forty patients (mean age, 59.0 years; 60.7% male) underwent subtotal gastrectomy with B-I (65.0%), B-II (27.1%), Roux-en-Y (4.3%), jejunal interposition (0.7%), or proximal gastrectomy (4.3%). Preoperative presence of AG (62.9%) and IM (72.9%) was confirmed. The mean period between surgery and the last endoscopic follow-up was 38.0±25.6 months. Of the 140 patients, 80 (57.1%) were found to be persistently positive for *H. pylori*, and 60 (42.9%) showed spontaneous negative conversion at least once during follow-up. Of these 60 patients, eight (13.3%) showed more complex postoperative dynamic changes between negative and positive results. The spontaneous negative conversion group showed a trend of having more postoperative IM compared to the persistent *H. pylori* group. **Conclusions:** A high percentage of spontaneous regression and complex dynamic changes in *H. pylori* status were observed after partial gastrectomy, especially in individuals with postoperative histological IM. It is better to consider postoperative eradication therapy after retesting for *H. pylori*.
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Key Words: *Helicobacter pylori*; Postoperation; Eradication

INTRODUCTION

Gastric cancer had been the most common cause of cancer deaths worldwide until the 1990s.[1] Although decreasing trends in incidence and mortality rates have been observed, stomach cancer is still the second leading cause of cancer death worldwide.[2,3] Chronic infection with *Helicobacter pylori* is the strongest identified risk factor for stomach cancer with worldwide attributable fraction reaching 89.0%.[4] In addition, the prophylactic effect of *H. pylori* eradication on development of metachronous cancer after endoscopic resection of gastric cancer was reported.[5]

Asia-Pacific consensus guideline suggested that *H. pylori* screening and eradication in high-risk populations could probably reduce gastric cancer incidence.[6] Thus, *H. pylori* eradication in patients who underwent subtotal gastrectomy for gastric cancer is strongly recommended. However, there have been a few studies reporting spontaneous regression of *H. pylori* after subtotal gastrectomy in peptic ulcer disease and gastric cancer patients.[7,8] The changes in postoperative *H. pylori* infection status have been suggested to be related to bile reflux and dramatic change of acid secretion after the surgery, which appear to inhibit the growth of *H. pylori* in the remnant stomach.[8-11] The possibility of dynamic changes raises a question for clinicians about the need for "retesting" of postoperative *H. pylori* status.

From this background, the aim of the present study was to

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evaluate the postoperative changes of *H. pylori* detection and to analyze the factors which affect this dynamic changes of in *H. pylori* infection status after gastric cancer surgery.

MATERIALS AND METHODS

1. Subjects

Patients who underwent gastric cancer surgery at Seoul National University Bundang Hospital with positive *H. pylori* status at the time of cancer diagnosis between December 2010 and July 2014 were prospectively enrolled. All gastric cancer patients were histologically confirmed to have gastric adenocarcinoma by surgery. Subjects with a history of previous gastric cancer or gastric surgery, eradication therapy before surgery, severe concomitant illness, and treatment with steroids or non-steroidal anti-inflammatory drugs, use of proton pump inhibitors (PPI) or antibiotics within 4 weeks were excluded. Every enrolled patient underwent postoperative *H. pylori* status evaluation.

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital and written informed consent was obtained from all participants (IRB number: B-1510/320-116).

2. *H. pylori* tests and histology

Preoperatively, four biopsy specimens were obtained from the antrum and the mid body of the stomach, respectively. After surgery, three tissue samples from lesser curvature and greater curvature of remained body were biopsied. Both Campylobacter like organism (CLO) test and Giemsa stain were done on every patient pre- and postoperatively.

Tissue sections were stained with modified Giemsa to prove the presence of *H. pylori*. *H. pylori* status was additionally assessed by rapid urease test (CLO test; Delta West, Bentley, Australia) and culture studies. Protocols for the biopsy-based tests have been previously described in detail.[12] Specific immunoglobulin G (IgG) for *H. pylori* was screened by an enzyme-linked immunosorbent assay (ELISA) in each subject's serum (Genedia *H. pylori* ELISA; Green Cross Medical Science Corp., Eumsung, Korea); Korean strain was used as antigen in this *H. pylori* antibody test.[13] Each patient was asked about their history of *H. pylori* eradication. If all of these four tests and history of *H. pylori* eradication were negative, the subject was determined as *H. pylori*-negative status. Past infection was defined as being positive for *H. pylori* IgG or having the history of eradication with negative result of abovementioned three invasive tests. Degree of inflammatory cell infiltration, atrophic gastritis (AG), and intestinal metaplasia (IM) were confirmed by hematoxylin and eosin stain who was unaware of the patient history and endoscopic findings. The histological features of the gastric mucosa were recorded using an updated Sydney scoring system (i.e., 0=none, 1=slight, 2=moderate, and 3=marked).[14] When the specimens were not prepared well enough to correct evaluate full-thickness gastric mucosa due to problems such as improper fixation, inaccurate orientation, and section inappropriateness, or whenever inflammation prevented a clear distinction between

Table 1. Baseline Characteristics of 140 Patients with Biopsy-Confirmed Stomach Cancer

Variable	Value
Age, yr	59.0±11.54
Sex	
Male	85 (60.7)
Female	55 (39.3)
Lauren classification	
Intestinal	69 (49.3)
Diffuse	69 (49.3)
Mixed	2 (1.4)
EGC or AGC	
EGC	91 (65.0)
AGC	49 (35.0)
Cancer location	
Antrum	63 (45.0)
Body	65 (46.4)
Antrum and body	7 (5.0)
Cardia	5 (3.6)
Surgery type	
Subtotal gastrectomy	
Billroth I	91 (65.0)
Billroth II	38 (27.1)
Roux-en-Y	4 (4.3)
With jejunal interposition	1 (0.7)
Proximal gastrectomy	6 (4.3)
Smoking	
Never	57 (40.7)
Current	29 (20.7)
Ex-smoker	54 (38.6)
Alcohol	
None	69 (49.3)
Social	53 (37.9)
Heavy*	18 (12.9)
Atrophic gastritis	
Negative	34 (24.3)
Positive	88 (62.9)
Not applicable	18 (12.9)
Intestinal metaplasia	
Negative	38 (27.1)
Positive	102 (72.9)

Data are presented as mean±SD or number (%).
EGC, early gastric cancer; AGC, advanced gastric cancer.
*More than 200 g/wk.

non-atrophic and atrophic phenotypes samples were classified as inapplicable for atrophy.[15]

3. *H. pylori* eradication therapy and follow-up

The patients with persistent *H. pylori* infection after surgery received eradication therapy, consisting of a standard dose of a PPI twice a day, amoxicillin 1 g twice a day, and clarithromycin 500 mg twice a day for 1 week. Eradication of *H. pylori* was confirmed by ^{13}C urea breath test (UBT), which took place 4 weeks after the completion of treatment. PPI was discontinued for 4 weeks before UBT. In addition, the follow-up endoscopy was done every year after the eradication of *H. pylori*. Three biopsy-based tests to evaluate *H. pylori* and histological grading of AG and IM were performed as noted above. Spontaneous *H. pylori*-negative conversion was defined as all of the histology findings for *H. pylori* were negative at least once during the follow-up period after surgery. "Dynamic changes" means the presence of another change in *H. pylori* status after being confirmed as "spontaneous negative conversion."

4. Statistical analysis

All statistical analyses were performed using the SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). Student t-test and chi-square test were used to compare the baseline characteristics between persistently positive- and spontaneous negative conversion group. To assess the factors related with postoperative *H. pylori* status, student t-test, chi-square test, and Fisher exact test were performed. Differences were considered significant when p-values were <0.05.

RESULTS

1. Baseline characteristics

A total of 140 biopsy proven stomach cancer patients (mean age, 59.0 years; 85 male [60.7%]) with known *H. pylori* status at the time of diagnosis were enrolled (Table 1). Every patient on baseline was found to be positive on at least one out of three *H. pylori* tests (CLO test, Giemsa stain, or *H. pylori* IgG). *H. pylori* IgG the test was done on 80 patients (57.1%) at the time of enrollment. Among them, three patients showed negative result for the serologic test.

All patients had undergone gastrectomy (subtotal gastrectomy with B-I, 91 [65.0%]; B-II, 38 [27.1%]; Roux-en-Y, 4 [4.3%]; jejunal interposition, 1 [0.7%]; proximal gastrectomy, 6 [4.3%]). There were 69 (49.3%) of intestinal and 69 (49.3%) of diffuse type cancers according to Lauren classification. Mean size of cancer lesion was 3.79±2.3 cm. Histologic AG and IM were confirmed to be present (AG, 88 [62.9%]; IM, 102 [72.9%]) before surgery.

2. Postoperative endoscopic follow-up

After surgery, annual follow-up was planned, and all 140 patients underwent endoscopy at least once (up to seven times). Forty-four patients (31.5%) were followed up more than twice. The mean interval between surgery and the first follow-up was 25.3±19.8 months. Mean follow-up period between surgery and the last endoscopic follow up was 38.0±25.6 months (Table 2).

Table 2. Postoperative Endoscopic Follow-Up Sessions

No. of follow-up times	No. (%)
Up to 1st time	96 (68.6)
Up to 2nd time	19 (13.6)
Up to 3rd–7th time	25 (17.9)

Mean period between surgery and the last endoscopic follow-up: 38.0±25.6 months.

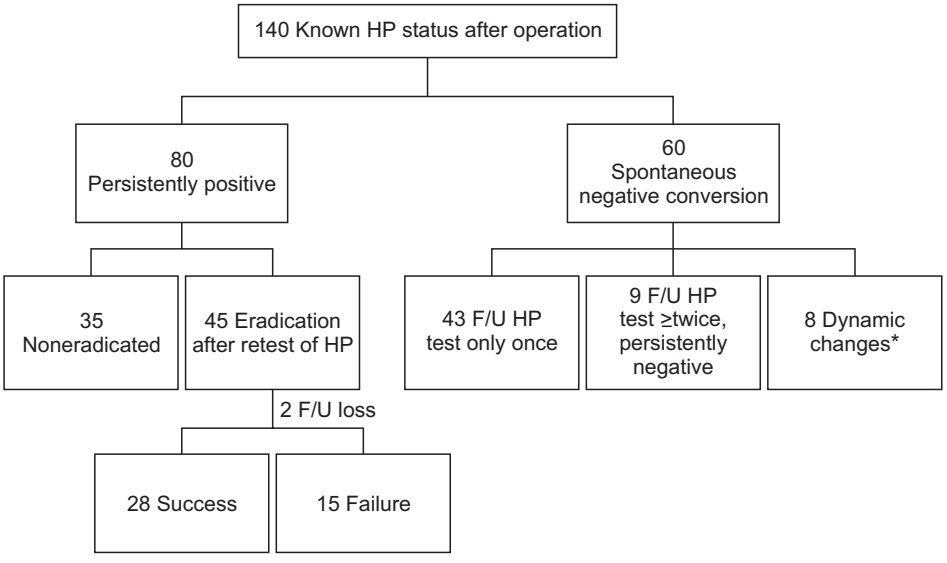

Fig. 1. Flow chart of the *Helicobacter pylori* status of 140 patients with biopsy-confirmed stomach cancer. Every patient who underwent surgery was retested for *Helicobacter pylori*, postoperatively.
HP, *Helicobacter pylori*; F/U, follow-up.
*Dynamic changes between negative and positive *H. pylori*.

3. Eradication therapy after surgery

All patients had their *H. pylori* status rechecked with both CLO test and Giemsa stain after surgery, before making decision regarding eradication therapy. Among them, 80 patients (57.1%) were found to be persistently positive and 45 of them underwent eradication therapy with success rate of 62.2% (Fig. 1). Sixty patients (42.9%) showed spontaneous negative conversion at least once during the follow-up period with negative test results from both CLO test and Giemsa stain. Dynamic changes between negative and positive results were noted in eight patients (5.7%), who were included in the spontaneous negative conversion group.

4. Spontaneous *H. pylori*-negative conversion rate after surgery and dynamic changes of *H. pylori*

After surgery, 60 patients (42.9%) showed spontaneous *H. pylori*-negative conversion among 140 patients who underwent endoscopy at least once (up to seven times) (Fig. 1). Among the 60 patients, 43 patients (71.6%) were followed-up only once and nine patients (15%) received endoscopy at least twice. In case of eight patients (13.3%), *H. pylori* status showed more complex

Table 3. Comparison of Persistently *Helicobacter pylori*-Positive and -Negative Conversion Groups after Surgery (n=140)

Variable	Negative conversion* (n=60)	Persistently positive (n=80)	p-value
Surgery			0.261
Subtotal B-I	34 (56.7)	57 (71.3)	
Subtotal B-II	20 (33.3)	18 (22.5)	
Subtotal Roux-en-Y	2 (3.3)	2 (2.5)	
Subtotal with jejunal interposition	0	1 (1.3)	
Proximal gastrectomy	4 (6.7)	2 (2.5)	
Age, yr	58.95±11.09	59.09±11.93	0.944
Male sex	36 (60.0)	49 (61.3)	1.000
Smoking			0.168
Never	22 (36.7)	35 (43.8)	
Current	17 (28.3)	12 (15.0)	
Ex-smoker	21 (35.0)	33 (41.3)	
Alcohol			0.971
None	30 (50.5)	39 (48.8)	
Social	22 (36.7)	31 (38.8)	
Heavy	8 (13.3)	10 (12.5)	
Atrophic gastritis (baseline)			0.677
Negative	16 (26.7)	18 (22.5)	
Positive	38 (63.3)	50 (62.5)	
Inapplicable	6 (10.0)	12 (15.0)	
Atrophic gastritis (1st follow-up)			0.008†
Negative	32 (53.3)	36 (45.0)	
Positive	8 (13.3)	20 (25.0)	
Inapplicable	20 (33.3)	16 (20.0)	
Not available	0	8 (10.0)	
Intestinal metaplasia (baseline)			0.340
Negative	19 (31.7)	19 (23.8)	
Positive	41 (68.3)	61 (76.3)	
Intestinal metaplasia (1st follow-up)			0.001†
Negative	38 (63.3)	59 (73.8)	
Positive	22 (36.7)	13 (16.3)	
Not available	0	8 (10.0)	

Data are presented as number (%) or mean±SD.
*Spontaneous conversion to *H. pylori*-negative status at least once during follow-up period; †Statistically significant correlations ($p<0.05$).

dynamic changes between negative and positive results at each follow-up (Fig. 1).

5. Comparison between persistently *H. pylori*-positive group and spontaneous *H. pylori*-negative conversion group after surgery

We compared variables between the patients who had persistent *H. pylori* infection (n=80, 57.1%) and those with spontaneous negative conversion (n=60, 42.9%) after gastrectomy. There was no statistically significant difference in age, gender, surgery type, alcohol consumption or cigarette smoking between two groups.

The distribution for the presence of AG and IM was not different between two groups at the baseline biopsy. However, there were significant changes based on the first postoperative biopsy results (Table 3). Spontaneous negative conversion group showed trend of having more IM compared to the *H. pylori* persistent group. However, in case of AG, it showed a reversed result. There were 20 (33.3%) and 16 (20.0%) inapplicable cases in the negative conversion group and in the persistently positive group, respectively (Table 3).

DISCUSSION

It is controversial whether *H. pylori* eradication is effective in the prevention of gastric cancer in postgastrectomy patients.[5,16] However, most guidelines include early gastric cancer as an indication for *H. pylori* eradication based on the reports regarding the prevention of metachronous cancer.[5,6,17] Although the effect of subtotal gastrectomy on *H. pylori* infection status has not been fully evaluated, some reports suggested spontaneous regression of *H. pylori* after partial gastrectomy in patients with peptic ulcer disease and gastric cancer.[7,9] Furthermore, the prevalence of *H. pylori* infection or colonization was significantly lower in the group who underwent distal gastrectomy than that of the control group in peptic ulcer patients.[7] As bile reflux is more severe in remnant stomach after distal gastrectomy than in control, it might be the cause for the lower rate of *H. pylori* infection.[8,9] In addition, some studies suggested that the spontaneous *H. pylori* clearance was related to the type of gastric reconstruction procedures and the time after the operation. That is, Billroth-II procedure had a higher bile reflux rate and a lower *H. pylori* infection prevalence than the Billroth-I procedure.[18] In contrast, there have been reports on *H. pylori* reinfection after partial gastrectomy in benign diseases,[19] and the remnant mucosa after gastric resection for duodenal ulcer and gastric cancer was suggested to be a favorable environment for *H. pylori* infection.[20] These various reports necessitate further investigation on the natural course of *H. pylori* status after gastric surgery.

In the present study, spontaneous negative conversion of *H. pylori* frequently occurred in patients who had not received the eradication therapy after partial gastrectomy. It is in accordance with the earlier studies showing that almost 40% of patients had spontaneous regression postoperatively.[8,11] However, *H. pylori* status could fluctuate due to the limitation of *H. pylori* tests especially in the background of atrophy and IM.[12] Previous studies have shown the limitations of invasive and noninvasive tests in detecting *H. pylori* infection in patients with AG and IM.[21-23] The bacterial load of *H. pylori* decreases as the gastric atrophy and IM progresses,[23] and sparse bacteria have uneven distribution in the stomach. Our result shows that postoperative histology in the spontaneous negative conversion group showed more IM than persistently positive group, supporting this harsh environment of IM kicks out the *H. pylori* spontaneously. However, atrophy (loss of appropriate glands) showed reverse results to the IM and it might be originated high proportion of inapplicable cases. In addition, the possibility of false negative results in the AG or IM could have been existed because the distribution is not even, especially adequately interpreted cases for histologic atrophy was so small.

In our study, there was no significant difference between spontaneous conversion and persistently positive groups according to surgery type, which could affect the bile reflux. It could suggest that IM could be a more important factor for the survival of *H. pylori* than bile reflux.

As remnant stomach has different anatomic and biological environment, there have been several studies to investigate the efficacy of postoperative eradication therapy.[11,24-27] However, the number of subjects in those studies was relatively small, and the time from the operation to the eradication therapy was too long. Moreover, eradication regimen in some studies is not applicable nowadays because PPI based dual therapy was used instead of PPI-based triple therapy in the earlier studies.[24,25] In addition, it is sometimes difficult to interpret the eradication in the gastric remnant as dynamic changes frequently occur. Therefore, careful serial follow-up is necessary to define "true spontaneous regression."

The present study is a comprehensive study with relatively long duration of follow-up around 3 years. It also confirmed *H. pylori* status with serial multiple methods including histology with modified Giemsa stain and CLO test for all the subjects. However, our study also has limitation of being conducted as a single-center study with relatively small number of patients even the inclusion period lasted nearly 4 years. In addition, among 60 patients who had spontaneous negative conversion, 43 (72%) subjects were followed up only once. If they had been tested more times, dynamic changes might have been described. Another limitation is that we have not analyzed in detail regarding the effect of cancer chemotherapy on the dynamic change of *H. pylori*. That is, we did not collect the exact data and analyzed the effect even though most of the patients with advanced gastric cancer (49 subjects, 35% of the enrolled patients) had undergone adjuvant chemotherapy. However, as chemotherapeutic agents are not antibiotics and the proportion

of advanced gastric cancer was rather small in this study, we suppose its role might be minor in the spontaneous negative conversion than IM.

In conclusion, we observed that there was relatively high percentage of spontaneous regression and dynamic changes in status of *H. pylori* after partial gastrectomy, with a trend of having more histologic IM. Postoperative *H. pylori* eradication therapy had better be performed after retest for *H. pylori*, and sometimes serial follow-up tests are necessary before decision.

CONFLICTS OF INTEREST

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

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