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*. (Gut Liver 2017;11:209-215)

**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.7-9 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...
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. 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. 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).

### 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 (3.3)     |
| 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.\textsuperscript{15}

3. \textit{H. pylori} eradication therapy and follow-up

The patients with persistent \textit{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 \textit{H. pylori} was confirmed by \textsuperscript{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 \textit{H. pylori}. Three biopsy-based tests to evaluate \textit{H. pylori} and histological grading of AG and IM were performed as noted above. Spontaneous \textit{H. pylori}–negative conversion was defined as all of the histology findings for \textit{H. pylori} were negative at least once during the follow-up period after surgery. “Dynamic changes” means the presence of another change in \textit{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 \textit{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 \textit{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 \textit{H. pylori} tests (CLO test, Giemsa stain, or \textit{H. pylori} IgG). \textit{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).

\begin{table}[h]
\centering
\caption{Postoperative Endoscopic Follow-Up Sessions}
\begin{tabular}{ll}
\hline
No. of follow-up times & No. (%) \\
\hline
Up to 1st time & 96 (68.6) \\
Up to 2nd time & 19 (13.6) \\
Up to 3rd–7th time & 25 (17.9) \\
\hline
\end{tabular}
\end{table}

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

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig1.png}
\caption{Flow chart of the \textit{Helicobacter pylori} status of 140 patients with biopsy-confirmed stomach cancer. Every patient who underwent surgery was restested for \textit{Helicobacter pylori}, postoperatively. \textit{HP}, \textit{Helicobacter pylori}; F/U, follow-up. \textsuperscript{*}Dynamic changes between negative and positive \textit{H. pylori}.}
\end{figure}
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                                                       |                           |                             |         |
| Subtotal B-I                                                 | 34 (56.7)                 | 57 (71.3)                   | 0.261   |
| 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 gastrectomy patients. However, most guidelines include early gastric cancer as an indication for H. pylori eradication based on the reports regarding the prevention of metachronous cancer. 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. 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. 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. 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. In contrast, there have been reports on H. pylori re-infection after partial gastrectomy in benign diseases, and the remnant mucosa after gastric resection for duodenal ulcer and gastric cancer was suggested to be a favorable environment for H. pylori infection. 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. However, H. pylori status could fluctuate due to the limitation of H. pylori tests especially in the background of atrophy and IM. Previous studies have shown the limitations of invasive and noninvasive tests in detecting H. pylori infection in patients with AG and IM. The bacterial load of H. pylori decreases as the gastric atrophy and IM progresses, 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. 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. 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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