Effect of *Helicobacter pylori* Eradication on Subsequent Dysplasia Development after Endoscopic Resection of Gastric Dysplasia

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**Background/Aims:** Eradication of *Helicobacter pylori* reduces the incidence of gastric cancer, and may inhibit gastric dysplasia progression into gastric cancer. The aim of this study was to investigate the effect of eradication of *Helicobacter* on the incidence of subsequent gastric dysplasia development after endoscopic resection.

**Methods:** Medical records of patients who underwent endoscopic resection for gastric dysplasia were retrospectively reviewed. Presence of *H. pylori* was assessed by the Campylobacter-like organism test and histology. The rate of subsequent dysplasia development after endoscopic resection between the eradication group and non-eradication group was compared.

**Results:** Total of 129 patients positive for *H. pylori* infection were included for analysis. Of these, 85 patients received successful eradication therapy and 44 patients did not receive eradication therapy or failed to achieve successful eradication. Sex, mean age and pathologic grade of dysplasia did not differ between the two groups. In univariate analysis, the grade of intestinal metaplasia (*p*=0.013) significantly differed between metachronous dysplasia group and non-metachronous dysplasia group. In multivariate analysis, eradication of *H. pylori* (*p*=0.014) was related to reduced incidence of subsequent gastric dysplasia development after endoscopic resection.

**Conclusions:** Eradication of *H. pylori* likely has a beneficial effect in preventing the development of subsequent gastric dysplasia, a premalignant lesion of gastric cancer, after endoscopic resection. *(Korean J Gastroenterol 2013;61:307-312)*

**Key Words:** *Helicobacter pylori*; Gastric dysplasia; Disease eradication; Endoscopic resection

**INTRODUCTION**

*Helicobacter pylori* infection is a well-established cause of gastric cancer worldwide. It is believed that *H. pylori* causes gastric cancer progressively starting from atrophic gastritis to intestinal metaplasia, dysplasia, and finally cancer. Gastric dysplasia is defined as noninvasive neoplastic proliferation of the gastric epithelium without evidence of tissue invasion, characterized by histologic alteration. As it represents the penultimate stage of gastric carcinogenesis, endoscopic resection is recommended. A previous study from Japan suggested that eradication of *H. pylori* after endoscopic resection of early gastric cancer has a prophylactic effect on the development of metachronous gastric cancer. Although gastric dysplasia is considered to be a premalignant lesion of gastric cancer and its development is thought
to be closely linked to *H. pylori* infection, the effect of eradication of *H. pylori* on the natural course of gastric dysplasia remains largely unknown. Moreover, no study has assessed the effect of eradication of *H. pylori* after endoscopic resection of gastric dysplasia.

The present study was undertaken to determine the effect of eradication of *H. pylori* on the development of gastric dysplasia after endoscopic resection of the affected lesions.

**SUBJECTS AND METHODS**

1. Patients

This was a retrospective study that reviewed medical records for patient selection. Patients who had undergone endoscopic resection at the Seoul National University Bundang Hospital (Seongnam, Korea) between August 2003 and March 2011 (*n*=1,083) were assessed for enrollment. Patients were eligible for enrollment if they were diagnosed with gastric dysplasia and had undergone endoscopic resection. Patient selection criteria is shown in Fig. 1. Endoscopic resection included both endoscopic mucosal resection (EMR) and endoscopic submucosal dissection. We defined metachronous dysplasia as dysplasia subsequently detected in different location more than one year after endoscopic resection of the first lesion. Exclusion criteria were previous history of gastric cancer, previous gastric surgery, positive resection margin, absence of active *H. pylori* infection, endoscopic resection performed for lesions other than dysplasia such as benign gastric polyp, dysplasias detected within one year on follow-up endoscopy, and absence of follow-up endoscopy after endoscopic resection. All patients had given their written informed consent, and this study was approved by the institutional review board of Seoul National University Bundang Hospital.

2. Determination of *H. pylori* infection status and eradication of bacterium

To assess the *H. pylori* infection status, the rapid urease test (Campylobacter-like organism test; Delta West, Bently, WA, Australia) and histologic evaluation of biopsy samples taken during endoscopy were used. Patients were regarded as currently *H. pylori*-infected when both tests showed positive results. Those who received an antimicrobial treatment were given the standard triple therapy of the standard dose proton pump inhibitor (PPI) and 500 mg of clarithromycin twice daily and 1 g of amoxicillin twice daily for 7 days as the

| Patients undergone endoscopic resection (Aug 2003-March 2011; *N*=1,083) |
|-----------------------------|
| Pathology other than adenoma (*n*=562) |
| Endoscopic resection for gastric adenoma (*n*=521) |
| Positive resection margin (*n*=139) |
| Adenoma detected within one year on follow-up endoscopy (*n*=100) |
| Adenoma recurring on resection site (*n*=12) |
| Loss to follow-up (*n*=72) |
| Patients tested for *Helicobacter pylori* (*n*=198) |
| Negative for *Helicobacter pylori* (*n*=69) |
| 129 patients were eligible for analysis |
| Successful eradication group (*n*=85) |
| Persistent infection group |
| Non-eradication (*n*=37) |
| Failed eradication (*n*=7) |

Fig. 1. Patient selection criteria.
first-line therapy. Thereafter, patients were given ulcer medications for 8 weeks to treat iatrogenic ulcer. After 4 weeks, eradication was evaluated using the urea breath test. If eradication was not achieved, a quadruple therapy (standard dose PPI twice daily, 500 mg tetracycline qid daily, 500 mg metronidazole tid daily, 300 mg tripotassium dicitrato bismuth three times daily for 7 days) was given as the second line-therapy. After second line-therapy, patients were re-assessed with the urea breath test to confirm eradication. Only those who had successfully achieved eradication were included for analysis. Patients who did not achieve eradication after second line-therapy were included as control in persistent infection group.

3. Histologic evaluation

Biopsy specimens were examined by two expert pathologists, and histologic criteria of intestinal metaplasia and dysplasia were graded according to the updated Sydney system and the Vienna classification, respectively. Intestinal metaplasia was graded by biopsy specimens taken from antrum and body of each subjects. Low-grade dysplasia (category 3) and high-grade dysplasia (category 4) were included in the study.8,9 The size of dysplasia was measured using endoscopically resected tissue and applied in the analysis. Patients were followed-up regularly with endoscopy every 3-12 months after endoscopic resection and biopsy was done at sites suspected of harboring metachronous dysplastic lesions. New dysplasia occurring at the previously resected site was considered as recurrence and the associated data were censored.

4. Statistical analyses

Categorical variables were analyzed by the chi-square test. Continuous variables were analyzed by the Student’s t-test. Univariate analysis was done by the Student’s t-test and chi-square test and multivariate analysis was done using all the variables. Statistical significance was set at 0.05. Cumulative survival was estimated by Cox’s proportional hazards model. All statistical analyses were performed by using PASW Statistics software version 18.0 (IBM Co., Armonk, NY, USA).

RESULTS

A total of 1,083 patients were assessed for eligibility, and 129 patients were included for analysis. Patients were divided into two groups based on whether they received successful eradication therapy for H. pylori (n=85) or not (n=44). The baseline characteristics of these groups are summarized in Table 1. There were no significant differences between the successful eradication group and persistent infection group in terms of age, sex, location and size of dysplasia, degree of intestinal metaplasia, and duration of follow-up after endoscopic resection. New gastric dysplasia was detected in four patients (4.7%) in the successful eradication group and in five patients (11.4%) in the persistent infection group after endoscopic resection.

### Table 1. Baseline Characteristics of Patients and Lesions according to Eradication Status

| Characteristic                             | Successful eradication group (n=85) | Persistent infection group (n=44) | p-value |
|-------------------------------------------|-------------------------------------|----------------------------------|---------|
| Mean age (yr)                             | 59.89±9.10                          | 62.82±8.39                       | 0.078   |
| Sex                                       |                                     |                                  | 0.611   |
| Female                                    | 28 (32.9)                           | 16 (36.4)                        |         |
| Male                                      | 57 (67.1)                           | 28 (63.6)                        |         |
| Location of dysplasia                     |                                     |                                  | 0.837   |
| Antrum                                    | 62 (72.9)                           | 31 (70.5)                        |         |
| Body                                      |                                     |                                  |         |
| Lower                                     | 19 (22.4)                           | 12 (27.3)                        |         |
| Mid                                       | 2 (2.4)                             | 1 (2.3)                          |         |
| Upper                                     | 2 (2.4)                             | 0 (0)                            |         |
| Size of dysplasia (mm³)                   | 104.82±181.73                       | 88.80±93.59                      | 0.585   |
| Degree of intestinal metaplasia           |                                     |                                  | 0.087   |
| None                                      | 17 (20.0)                           | 7 (15.9)                         |         |
| Mild                                      | 21 (24.4)                           | 9 (20.5)                         |         |
| Moderate                                  | 29 (34.1)                           | 15 (34.1)                        |         |
| Marked                                    | 14 (16.5)                           | 4 (9.1)                          |         |
| Unknown                                   | 4 (4.7)                             | 9 (20.5)                         |         |
| Histologic grade of dysplasia             |                                     |                                  | 0.200   |
| Low                                       | 76 (89.4)                           | 43 (97.7)                        |         |
| High                                      | 8 (9.4)                             | 1 (2.3)                          |         |
| Unknown                                   | 1 (1.2)                             | 0 (0)                            |         |
| Mean duration of follow-up (mo)           | 42.99±20.31                         | 36.00±20.85                      | 0.069   |
| Metachronous dysplasia                    | 4 (4.7)                             | 5 (11.4)                         | 0.272   |

Values are presented as mean±SD or n (%).
Table 2. Comparison of Baseline Characteristics of Patients and Lesions between Those Who Developed Metachronous Dysplasia and Who Did Not

| Characteristic | Metachronous dysplasia group (n=9) | Non-metachronous dysplasia group (n=120) | p-value |
|---------------|------------------------------------|------------------------------------------|---------|
| Mean age (yr) | 64.44±10.35                        | 60.63±8.82                               | 0.218   |
| Sex           |                                    |                                          |         |
| Female        | 1 (11.1)                           | 43 (35.8)                                | 0.165   |
| Male          | 8 (88.9)                           | 77 (64.2)                                |         |
| Location of dysplasia |                                |                                          |         |
| Antrum        | 5 (55.6)                           | 88 (73.3)                                | 0.464   |
| Body          |                                    |                                          |         |
| Lower         | 4 (44.4)                           | 27 (22.5)                                |         |
| Mid           | 0 (0)                              | 3 (2.5)                                  |         |
| Upper         | 0 (0)                              | 2 (1.7)                                  |         |
| Size (mm^3)   | 94.32±119.89                       | 99.74±159.91                             | 0.921   |
| Degree of intestinal metaplasia |                        |                                          |         |
| None          | 0 (0)                              | 24 (20.0)                                |         |
| Mild          | 1 (11.1)                           | 29 (24.2)                                |         |
| Moderate      | 3 (33.3)                           | 41 (34.2)                                |         |
| Marked        | 5 (55.6)                           | 13 (10.8)                                |         |
| Unknown       | 0 (0)                              | 13 (10.8)                                |         |
| Histologic grade |                                |                                          |         |
| Low           | 9 (100.0)                          | 110 (91.7)                               | >0.999  |
| High          | 0 (0)                              | 9 (7.5)                                  |         |
| Unknown       | 0 (0)                              | 1 (0.8)                                  |         |
| Successful eradication |                      |                                          |         |
|               | 5 (41.6)                           | 81 (67.5)                                | 0.110   |
|               |                                    |                                          | 0.014   |

Values are presented as mean±SD or number (%).

Fig. 2. Effect of *Helicobacter pylori* eradication on time to development of metachronous dysplasia.

eradication group and the persistent infection group (hazard ratio=0.143, p=0.008) (Fig. 2).

**DISCUSSION**

Gastric premalignant lesions are commonly detected during routine endoscopy, but guidelines for follow-up or surveillance of such lesions are still lacking. Prevalence of gastric dysplasia varies between 9% to 20% in high-risk areas for gastric cancers and up to 9.3% even in asymptomatic subjects without indication for esophagogastroduodenoscopy. According to a recently published guideline in the management of gastric precancerous lesions, both low-grade and high-grade dysplasia defined endoscopically, should be considered for endoscopic resection because of the possibility of upgraded histologic diagnosis after EMR. Considering the high incidence of gastric cancer in the country and the possibility of dysplasia progression into cancer, endoscopic resection is widely performed for precancerous lesions.

The natural course of gastric premalignant lesions, especially dysplasia, is not well established. Previous studies re-
ported that the local recurrence rate after EMR for early gastric cancer ranged between 2% and 35% and showed a higher curability and lower recurrence rate in en-bloc resection, rather than in piecemeal resection.\textsuperscript{1,13} However, there is no data regarding the recurrence rate of gastric dysplasia after endoscopic resection. To exclude the possibility of residual dysplasia being diagnosed as a new lesion, we only included patients with clear resection margin in the analysis. This inclusion criterion would have also minimized the influence of individual physician’s endoscopic skill on therapeutic outcome. \textit{H. pylori} causes chronic active gastritis, which progresses through the carcinogenic cascade of atrophic gastritis, intestinal metaplasia and dysplasia into gastric adenocarcinoma.\textsuperscript{14} There was statistical significance between the degree of intestinal metaplasia and metachronous dysplasia development in univariate analysis and this carcinogenic cascade can be the explanation. Although multivariate analysis showed no correlation between the degree of intestinal metaplasia and metachronous dysplasia (p=0.104), larger sample size could show different results.

Whether eradication of \textit{H. pylori} can arrest or reverse carcinogenesis in premalignant gastric lesions remains controversial. Some studies suggest that it leads to an improvement in gastric histology or even inhibition of gastric dysplasia progression into cancer.\textsuperscript{15-18} In our study, multivariate analysis showed that eradication of \textit{H. pylori} can significantly inhibit the development of subsequent dysplasia after endoscopic resection of gastric dysplasia. When compared by Cox' proportional hazard model, the hazard ratio of developing dysplasia treatment.

There are some limitations to our study. First, this was a retrospective, single-institutional study with a small sample size, so the results cannot be generalized. But according to Trautmann et al.,\textsuperscript{19} the recruitment of control group is difficult in gastric cancer prevention studies because \textit{Helicobacter}-infected patients expect antimicrobial therapy rather than being in the control group. In Korea, gastric cancer is one of the most common primary cancer and therefore, patients diagnosed of \textit{Helicobacter} infection are very willing to receive antimicrobial therapy even in the absence of strongly recommended indications for eradication therapy due to concerns of developing gastric cancer.\textsuperscript{20} A prospective study in this setting would be extremely difficult to conduct. Second, since there is no established guidelines concerning eradication of \textit{H. pylori} in gastric dysplasia, no specific eradication protocol existed for this study concerning who to treat, and eradication was performed based on the physician’s preference or at patient’s will. Considering this was a retrospective study, selection bias could have been occurred. Third, although the median follow-up period after eradication was relatively long (median of 36 months), taking into account that other studies investigating the effect of eradication of \textit{H. pylori} on gastric premalignant lesion had conflicting results may be due to the short follow-up periods.\textsuperscript{21,22} Thus, a more sufficient follow-up time may be needed to evaluate the long-term effect of eradication therapy on gastric dysplasia. But in our present study, we focused on the outcome itself rather than on changes over time.

Despite these limitations, this study demonstrates noteworthy findings as the first study to investigate the effect of eradication of \textit{H. pylori} on the incidence of subsequent metachronous gastric dysplasia development after endoscopic resection. Our results demonstrate that eradication of \textit{H. pylori} is beneficial in reducing the incidence of subsequent gastric dysplasia after endoscopic resection of gastric dysplasia. As gastric dysplasia is a premalignant lesion of gastric cancer and the preventive effect of eradication of \textit{H. pylori} in such patients are yet to be clarified, more well-designed, randomized controlled trials are warranted for the assessment of the long-term benefits of the treatment. If the present findings are confirmed, this could have great implications on gastric dysplasia treatment.

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