저작자표시-비영리-변경금지 2.0 대한민국

이용자는 아래의 조건을 따르는 경우에 한하여 자유롭게

- 이 저작물을 복제, 배포, 전송, 전시, 공연 및 방송할 수 있습니다.

다음과 같은 조건을 따라야 합니다:

저작자표시. 귀하는 원저작자를 표시하여야 합니다.

비영리. 귀하는 이 저작물을 영리 목적으로 이용할 수 없습니다.

변경금지. 귀하는 이 저작물을 개작, 변형 또는 가공할 수 없습니다.

- 귀하는 이 저작물의 재이용이나 배포의 경우, 이 저작물에 적용된 이용허락조건을 명확하게 나타내야 합니다.
- 저작권자로부터 별도의 허가를 받으면 이러한 조건들은 적용되지 않습니다.

저작권법에 따른 이용자의 권리는 위의 내용에 의하여 영향을 받지 않습니다.

이것은 이용허락규약(Legal Code)을 이해하기 쉽게 요약한 것입니다.

Disclaimer
Long-term effect of *Helicobacter pylori* eradication on metachronous gastric cancer development

2016년 10월

서울대학교 대학원

임상의과학과 전공

한승준
A thesis of the Master’s degree

Long-term effect of \textit{Helicobacter pylori} eradication on metachronous gastric cancer development

헬리코박터 제균치료가 후시성 위암 발생에 미치는 장기간의 영향

October 2016

The Department of Clinical Medical Sciences
Seoul National University
College of Medicine
Seung Jun Han
ABSTRACT

**Background:** Gastric mucosal atrophy and intestinal metaplasia by *Helicobacter pylori* infection are the main precursor lesions of gastric cancer. This study aims to evaluate the long-term effect of *Helicobacter pylori* eradication on the progression of precancerous lesions to metachronous cancer development after endoscopic resection of early gastric cancer.

**Methods:** The patients who underwent endoscopic resection of early gastric cancer were reviewed retrospectively. Changes in precancerous lesions and development of metachronous cancer were compared according to *Helicobacter pylori* eradication and final status of infection.

**Results:** In total, 565 patients were followed up for over 5 years after endoscopic resection of early gastric cancer. The grade of mucosal atrophy on corpus was significantly lower in the eradicated group than the persistent group during follow-up (p=0.029). In patients less than 70 years of age, the cumulative incidence rate of metachronous cancer was significantly lower in the *Helicobacter pylori*-eradicated group than the *Helicobacter pylori*-persistent group (p = 0.018). Age was an independent risk factor for metachronous cancer development.

**Conclusions:** *Helicobacter pylori* eradication might prevent the long-term development of metachronous cancer in younger patients by delaying the progression of precancerous lesions after endoscopic resection of early gastric cancer.
**Keywords:** *Helicobacter pylori*, Eradication, Gastric Cancer, Atrophy, Intestinal Metaplasia

**Student number:** 2015-22266
CONTENTS

Abstract ...............................................................................................................................................i
Contents........................................................................................................................................... iii
List of tables and figures .................................................................................................................iv

Introduction .......................................................................................................................................1
Material and Methods .....................................................................................................................3
Results...............................................................................................................................................6
Discussion .........................................................................................................................................21
References .........................................................................................................................................24
Abstract in Korean .............................................................................................................................28
LIST OF TABLES AND FIGURES

Table 1 Baseline characteristics ................................................................. 8
Table 2 Changes in histological grades of precancerous lesions .................. 13
Table 3 Baseline characteristics of patients with metachronous cancer ........ 16
Table 4 Risk factors for metachronous cancer development .......................... 20

Figure 1 The proportions of patients with precancerous lesions ................... 11
Figure 2 Cumulative incidence of metachronous cancer ............................... 18
INTRODUCTION

Gastric cancer is the third most common cause of cancer-related deaths worldwide (1). Early gastric cancer (EGC) is defined as a malignancy that does not invade deeper than the submucosa, irrespective of lymph node involvement (T1, any N). Endoscopic submucosal dissection (ESD) for EGC has been widely accepted as a standard treatment in Korea and Japan. However, periodic surveillance is necessary for detection of metachronous cancers even after curative ESD (2), (3).

*Helicobacter pylori* (*H. pylori*) infection results in gastric mucosal atrophy, intestinal metaplasia, dysplasia, and ultimately, cancer. Mucosal atrophy and intestinal metaplasia have been considered as precancerous lesions (4); however, whether precancerous lesions can be reversed by *H. pylori* eradication has not been fully clarified. Some systematic reviews reported that *H. pylori* eradication resulted in significant improvement of mucosal atrophy, whereas improvement of intestinal metaplasia was not seen (5-7). However, other recent studies reported a correlation between *H. pylori* eradication and improvement of intestinal metaplasia as well as mucosal atrophy (8-10).

Whether the eradication of *H. pylori* could prevent the development of metachronous cancer after endoscopic resection of EGC is controversial. In a 3-year prospective study, it was reported that the eradication of *H. pylori* after
endoscopic resection of EGC prevented the development of metachronous cancer (11). A meta-analysis showed that *H. pylori* eradication was successful in reducing the rate of metachronous gastric cancers (12). However, we reported that *H. pylori* eradication did not reduce the incidence of metachronous gastric lesions during a median follow-up period of 3 years after endoscopic treatment of EGC in a prospective randomized manner (13). Another study reported that the eradication of *H. pylori* did not prevent metachronous lesions, although *H. pylori* was a risk factor for the development of metachronous cancer after a median follow-up period of 39 months (14). Very few studies with a follow-up period longer than 5 years were conducted.

The aim of this study was to evaluate the long-term effect of *H. pylori* eradication on the progression of precancerous lesions to metachronous cancer development after ESD for EGC.
MATERIALS AND METHODS

Endoscopic submucosal dissection and follow-up endoscopic examination

All patients who underwent ESD for EGC between April 2005 and February 2011 were reviewed at Seoul National University Hospital. Indications for ESD included differentiated adenocarcinoma, tumor confined to the mucosa, gross tumor size no more than 2 cm in diameter, and no evidence of distant metastasis. The location of the lesions was divided into three portions according to the Japanese Classification of Gastric Cancer: upper, middle, and lower (15). In almost all cases, additional biopsy samples were obtained during ESD from two sites in the lesser curvature of the antrum and two sites in the lesser curvature of the corpus to test for the presence of *H. pylori* and to evaluate gastric mucosal atrophy and intestinal metaplasia using the updated Sydney System. Rapid urease test (CLO® test; Kimberly-Clark, UT, USA) was also performed. We included the patients reported in another paper of ours (13).

Follow-up endoscopic examination was scheduled at 3, 6, and 12 months and annually thereafter. *H. pylori* status and grades of gastric mucosal atrophy and intestinal metaplasia were evaluated in the same manner at all follow-up examinations. The follow-up duration was calculated as the interval between
ESD and the last endoscopic follow-up evaluation or the time of metachronous cancer development.

*H. pylori* status was considered positive if at least one test result (rapid urease test or histology) was positive. The patients without *H. pylori* infection during follow-up were classified as the negative group. The patients who underwent *H. pylori* eradication after ESD and confirmed negative for *H. pylori* during follow-up were defined as the eradicated group, and the patients in whom *H. pylori* were positive during follow-up regardless of whether they underwent *H. pylori* eradication were defined as the persistent group. Metachronous cancer was defined as the new carcinoma that occurred at another site in the stomach one year after ESD. Histological grades of mucosal atrophy and intestinal metaplasia were assigned according to the updated Sydney System, and compared between the groups.

The study was approved by the Ethics Committee of the Seoul National University Hospital (IRB no. H-1519-082-688) and was conducted in accordance with the Declaration of Helsinki.
Statistical analysis

Demographic data were compared using the independent t test or ANOVA test for variables with a parametric distribution, and Pearson’ chi-squared test or the Fisher’s exact test to compare the proportions. Changes in the histological grades of gastric mucosal atrophy and intestinal metaplasia were evaluated using the Mann-Whitney U test and Wilcoxon signed-rank test. The cumulative incidence of metachronous cancer was calculated using the Kaplan–Meier method, and compared between the groups were performed using the log-rank test. The statistical significance of metachronous cancer development according to variables was evaluated using Cox regression analysis. P-values less than 0.05 were considered to be statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 21.0 (SPSS, Chicago, IL).
RESULTS

Study population

In total, 783 patients who underwent ESD of EGC between April 2005 and February 2011 at Seoul National University Hospital were included. Patients were excluded from the analysis, if (1) they had a prior history of gastric cancer; (2) information was not available for *H. pylori* infection at the time of ESD; (3) there were no additional biopsy samples for the evaluation of precancerous lesions; (4) they had a recurring or synchronous lesion within 12 months after ESD; (5) they had a gastrectomy within 12 months after ESD; (6) they had a follow-up duration less than 12 months; and (7) they were older than 75 years.

In total, 565 patients were assessed for eligibility. The median follow-up periods for the negative group (157 patients), eradicated group (212 patients), and persistent group (196 patients) were 60, 61, and 60 months (range, 12-122 months), respectively. There were no significant differences between the groups in age, sex, location, size, depth of invasion, and tumor differentiation. The proportion of patients with corpus mucosal atrophy was significantly lower in the negative group than the eradicated and the persistent groups (*p* = 0.020). However, the proportion of patients with antral mucosal atrophy and intestinal metaplasia in both the antrum and corpus did not differ between the
groups (Table 1).
| Variables                             | Negative group | Eradicated group | Persistent group | P-value |
|--------------------------------------|---------------|-----------------|-----------------|---------|
|                                      | No            | No              | No              |         |
| Total                                | 157           | 212             | 196             |         |
| Mean age, years (SD)                 | 62.9 (8.1)    | 61.1 (8.1)      | 61 (9)          | 0.068   |
| Sex                                  |               |                 |                 |         |
| Male (%)                             | 131 (83.4)    | 165 (77.8)      | 144 (73.5)      | 0.081   |
| Female (%)                           | 26 (16.6)     | 47 (22.2)       | 52 (26.5)       |         |
| Location of tumor                    |               |                 |                 |         |
| Upper third (%)                      | 4 (2.5)       | 9 (4.2)         | 10 (5.1)        |         |
| Middle third (%)                     | 45 (28.7)     | 70 (33)         | 50 (25.5)       | 0.380   |
| Lower third (%)                      | 108 (68.8)    | 133 (62.7)      | 136 (69.4)      |         |
| Mean size of tumor, mm (SD)          | 18.3 (11.4)   | 18.3 (12.5)     | 17.9 (11.9)     | 0.932   |
| Depth of invasion of tumor           |               |                 |                 |         |
| Lamina propria (%)                   | 77 (49)       | 97 (45.8)       | 94 (48)         |         |
| Muscularis mucosa (%)                | 66 (42)       | 90 (42.5)       | 89 (45.4)       | 0.481   |
| Submucosa (%)                        | 14 (8.9)      | 25 (11.8)       | 13 (6.6)        |         |
| Well differentiated (%)               | 89 (56.7)     | 125 (59)        | 119 (60.7)      |         |
| Moderately differentiated (%)         | 62 (39.5)     | 80 (37.7)       | 69 (35.2)       | 0.925   |
| Histology of tumor                   |               |                 |                 |         |
| Poorly differentiated (%)             | 5 (3.2)       | 3 (1.4)         | 4 (2)           |         |
| Poorly cohesive (%)                  | 0             | 1 (0.5)         | 2 (1)           |         |
| Lauren's classification of tumor | Intestinal (%) | 152 (96.8) | 209 (98.6) | 189 (96.9) | 0.773 |
|---------------------------------|----------------|------------|------------|------------|-------|
| Diffuse (%)                     | 3 (1.9)        | 2 (0.9)    | 4 (2.1)    |            |       |
| None (%)                        | 38 (37.6)      | 43 (33.3)  | 34 (27.2)  |            |       |
| Mild (%)                        | 32 (31.7)      | 39 (30.2)  | 39 (31.2)  |            |       |
| Moderate (%)                    | 24 (23.8)      | 38 (29.5)  | 40 (32)    |            |       |
| Marked (%)                      | 7 (6.9)        | 9 (7)      | 12 (9.6)   |            |       |

| Antral mucosal atrophy | None (%) | 61 (55) | 52 (36.4) | 53 (38.7) |
|------------------------|----------|---------|-----------|-----------|
| Mild (%)               | 22 (19.8)| 41 (28.7)| 30 (21.9) |
| Moderate (%)           | 17 (15.3)| 39 (27.3)| 35 (25.5) |
| Marked (%)             | 11 (9.9)| 11 (7.7)| 19 (13.9) |

| Corpus mucosal atrophy | None (%) | 25 (16.4)| 32 (15.5) | 34 (17.9) |
|------------------------|----------|----------|-----------|-----------|
| Mild (%)               | 45 (29.6)| 47 (22.8)| 52 (27.4) |
| Moderate (%)           | 62 (40.8)| 89 (43.2)| 59 (31.1) |
| Marked (%)             | 20 (13.2)| 38 (18.4)| 45 (23.7) |

| Antral intestinal metaplasia | None (%) | 56 (37.6)| 66 (31.9)| 62 (33.2) |
|-------------------------------|----------|----------|-----------|-----------|
| Mild (%)                      | 33 (22.1)| 38 (18.4)| 34 (18.2) |
| Moderate (%)                  | 28 (18.8)| 61 (29.5)| 52 (27.8) |
| Marked (%)                    | 32 (21.5)| 42 (20.3)| 39 (20.9) |

| Corpus intestinal metaplasia | None (%) | 56 (37.6)| 66 (31.9)| 62 (33.2) |
|-----------------------------|----------|----------|-----------|-----------|
| Mild (%)                    | 33 (22.1)| 38 (18.4)| 34 (18.2) |
| Moderate (%)                | 28 (18.8)| 61 (29.5)| 52 (27.8) |
| Marked (%)                  | 32 (21.5)| 42 (20.3)| 39 (20.9) |

| Median follow-up duration, months (IQR) | 60.0 (44.5-74.5) | 61.0 (49.0-87.8) | 60.0 (48.0-78.0) |

No number, SD standard deviation, IQR interquartile range
Changes in gastric mucosal atrophy and intestinal metaplasia

Approximately 70% of patients had antral mucosal atrophy at the time of ESD. There were no significant differences in the proportion of patients with antral mucosal atrophy between the groups during follow-up. The initial proportion of patients with corpus mucosal atrophy did not differ significantly between the eradicated and the persistent group. At the last follow-up, corpus mucosal atrophy was more prominent in the persistent group than the eradicated and the negative groups ($p = 0.015$ and $< 0.001$, respectively). The proportions of patients with intestinal metaplasia did not differ between the groups during follow-up (Figure 1).

Although the mean histological grades for corpus mucosal atrophy did not differ between the eradicated and the persistent groups at baseline, it was significantly lower in the eradicated group than the persistent group at the last follow-up (1.03 vs. 1.29, respectively; $p = 0.029$). There were no significant differences in the grades of antral mucosal atrophy and intestinal metaplasia in both the antrum and the corpus between the groups during follow-up (Table 2).
Figure 1. The proportions of patients with precancerous lesions. (a) Antral mucosal atrophy at baseline; (b) Antral mucosal atrophy at the last follow-up;
(c) At baseline, the proportion of patients with corpus mucosal atrophy was higher in the eradicated group than in the negative group ($p = 0.011$); (d) At the last follow-up, the proportions of patients with corpus mucosal atrophy was higher in the persistent group than in the negative and the eradicated groups ($p < 0.001$ and $0.015$, respectively); (e) Antral intestinal metaplasia at baseline; (f) Antral intestinal metaplasia at the last follow-up; (g) Corpus intestinal metaplasia at baseline; (h) Corpus intestinal metaplasia at the last follow-up

$P$-values are greater than 0.05 unless otherwise stated.

Abbreviations: $N$ negative group, $E$ eradicated group, $P$ persistent group.
Table 2. Changes in histological grades of precancerous lesions

|                          | Baseline          |         | P-value       | The last follow-up |         | P-value       |
|--------------------------|-------------------|---------|---------------|--------------------|---------|---------------|
|                          | N  | E  | P  |               | N  | E  | P  |               |
| Mucosal atrophy, mean    |     |     |     |               |     |     |     |               |
| Antrum                  | 1  | 1.1| 1.24| 0.015 (N vs E)| 1.1| 1.46| 1.28| 0.013 (N vs E)|
| Corpus                  | 0.8| 1.06|1.15| 0.009 (N vs P)| 0.79|1.03| 1.29| <0.001 (N vs P)|
| Intestinal metaplasia, mean |     |     |     |               |     |     |     |               |
| Antrum                  | 1.51| 1.65|1.61|               | 1.68| 1.78| 1.69|               |
| Corpus                  | 1.24| 1.38|1.36|               | 1.16| 1.37| 1.3  |               |

Mann-Whitney U test
0 none, 1 mild, 2 moderate, 3 marked; according to the updated Sydney System

N negative group, E eradicated group, P persistent group

P-values are greater than 0.05 unless otherwise stated.
Development of metachronous gastric cancer

During a mean follow-up period of 63 months, metachronous gastric cancer had developed in 50 patients (50/565, 8.8%); 20 in the negative group (20/157, 12.7%), 12 in the eradicated group (12/212, 5.7%), and 18 in the persistent group (18/196, 9.2%). The incidence of metachronous cancer was lower in the eradicated group than the other groups without statistical significance \((p = 0.059)\). The median interval between ESD and the development of metachronous cancer was 36 months in the negative group, 52.5 months in the eradicated group, and 42.5 months in the persistent group. There were no significant differences in the baseline clinicopathologic characteristics of patients with metachronous cancer between the groups (Table 3).

In patients less than 70 years of age, Kaplan–Meier analysis showed that the cumulative incidence rate of metachronous cancer was significantly lower in the eradicated group than the negative and the persistent groups \((p = 0.001\) and 0.018, respectively) (Figure 2). In subgroup analyses of patients less than 65 years of age, the cumulative incidence rate of metachronous cancer development was consistently lower in the eradicated group than the negative and the persistent group \((p = 0.014\) and 0.031, respectively).

Cox regression analysis identified age to be an independent risk factor for metachronous cancer development (hazard ratio, 1.059, 95% confidence
interval, 1.001-1.120; \( p = 0.045 \)). Sex, grades of precancerous lesions and \( H. pylori \) status were not significant risk factors for metachronous cancer (Table 4).
Table 3. Baseline characteristics of patients with metachronous cancer

| Variables                  | Negative group | Eradicated group | Persistent group | P-value |
|----------------------------|----------------|------------------|------------------|---------|
| **Total**                  | 20             | 12               | 18               |         |
| **Mean age, years (SD)**   | 63.9 (7.8)     | 65.3 (8.4)       | 59.6 (8.6)       | 0.135   |
| **Sex**                    |                |                  |                  |         |
| Male (%)                   | 19 (95)        | 11 (91.7)        | 16 (88.9)        | 0.822   |
| Female (%)                 | 1 (5)          | 1 (8.3)          | 2 (11.1)         |         |
| **Location of tumor**      |                |                  |                  |         |
| Upper third (%)            | 0              | 0                | 1 (5.6)          | 0.888   |
| Middle third (%)           | 6 (30)         | 3 (25)           | 6 (33.3)         |         |
| Lower third (%)            | 14 (60)        | 9 (75)           | 11 (61.1)        |         |
| **Mean size of tumor, mm (SD)** | 17.6 (10.3) | 23.6 (14.0)     | 17.8 (7.0)       | 0.234   |
| **Depth of invasion of tumor** |              |                  |                  |         |
| Lamina propria (%)         | 10 (50)        | 4 (33.3)         | 9 (50)           |         |
| Muscularis mucosa (%)      | 7 (35)         | 7 (58.3)         | 9 (50)           | 0.383   |
| Submucosa (%)              | 3 (15)         | 1 (8.3)          | 0                |         |
| **Histology of tumor**     |                |                  |                  |         |
| Well differentiated (%)    | 11 (55)        | 5 (41.7)         | 11 (61.1)        |         |
| Moderately differentiated (%) | 8 (40) | 6 (50)           | 7 (38.9)         | 0.620   |
| Poorly differentiated (%)  | 1 (5)          | 0                | 0                |         |
| Poorly cohesive (%)        | 0              | 1 (8.3)          | 0                |         |
| Lauren's classification of tumor | Intestinal (%) | Diffuse (%) | None (%) | Mild (%) | Moderate (%) | Marked (%) | None (%) | Mild (%) | Moderate (%) | Marked (%) | None (%) | Mild (%) | Moderate (%) | Marked (%) | None (%) | Mild (%) | Moderate (%) | Marked (%) | None (%) | Mild (%) | Moderate (%) | Marked (%) |
|---------------------------------|----------------|-------------|----------|----------|--------------|------------|----------|----------|--------------|------------|----------|----------|--------------|------------|----------|----------|--------------|------------|----------|----------|--------------|------------|
| Intestinal (%)                  | 18 (95)        | 12 (100)    | 18 (100) |           | 0.999        |            | 0        | 0        | 0            |           | 2 (14.3) | 2 (10.5) | 7 (50)       | 1 (7.1)     | 8 (53.3) | 2 (13.3) | 4 (28.6)     | 1 (6.7)     | 2 (10.5) | 4 (22.2) | 6 (33.3)     | 3 (16.7)   |
| Diffuse (%)                     | 1 (5)          | 0           | 0        | 4 (50)   | 4 (33.3)     | 1 (12.5)   | 5 (62.5) | 2 (25)   | 3 (37.5)     | 1 (12.5)   | 1 (14.3) | 4 (26.7) | 3 (37.5)     | 2 (25)      | 4 (50)   | 5 (41.7) | 3 (37.5)     | 4 (26.7)    |
| None (%)                        | 2 (14.3)       | 0           | 0        | 4 (50)   | 4 (33.3)     | 1 (12.5)   | 5 (62.5) | 2 (25)   | 3 (37.5)     | 1 (12.5)   | 1 (14.3) | 4 (26.7) | 3 (37.5)     | 2 (25)      | 4 (50)   | 5 (41.7) | 3 (37.5)     | 4 (26.7)    |
| Mild (%)                        | 7 (50)         | 4 (50)      | 4 (33.3) | 4 (33.3) | 0.881        |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 2 (13.3) | 2 (10.5) | 8 (53.3)     | 1 (6.7)     | 4 (33.3) | 2 (16.7) | 4 (33.3)     | 1 (6.7)     |
| Moderate (%)                    | 4 (28.6)       | 3 (37.5)    | 4 (33.3) | 0.881    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 4 (26.7) | 2 (25)   | 8 (53.3)     | 1 (6.7)     | 5 (62.5) | 3 (25)   | 5 (62.5)     | 3 (25)      |
| Marked (%)                      | 1 (7.1)        | 1 (12.5)    | 2 (16.7) | 0.881    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 1 (7.1)  | 1 (12.5) | 5 (62.5)     | 1 (12.5)    | 5 (62.5) | 3 (25)   | 5 (62.5)     | 1 (12.5)    |
| None (%)                        | 8 (53.3)       | 0           | 3 (25)   | 0.881    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 2 (13.3) | 2 (10.5) | 8 (53.3)     | 1 (6.7)     | 5 (62.5) | 3 (25)   | 5 (62.5)     | 3 (25)      |
| Mild (%)                        | 2 (13.3)       | 5 (62.5)    | 3 (25)   | 0.087    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 2 (13.3) | 2 (10.5) | 5 (50)       | 2 (12.5)    | 4 (50)   | 5 (41.7) | 5 (41.7)     | 2 (12.5)    |
| Moderate (%)                    | 4 (26.7)       | 2 (25)      | 3 (25)   | 0.087    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 4 (26.7) | 3 (37.5) | 4 (26.7)     | 2 (25)      | 3 (37.5) | 4 (26.7) | 3 (37.5)     | 2 (25)      |
| Marked (%)                      | 1 (6.7)        | 1 (12.5)    | 3 (25)   | 0.087    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 1 (6.7)  | 1 (12.5) | 1 (6.7)      | 1 (12.5)    | 5 (62.5) | 3 (25)   | 5 (62.5)     | 3 (25)      |
| None (%)                        | 2 (10.5)       | 1 (8.3)     | 1 (5.9)  | 0.697    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 8 (42.1) | 5 (40.4) | 5 (26.3)     | 2 (16.7)    | 8 (42.1) | 5 (40.4) | 5 (26.3)     | 2 (16.7)    |
| Mild (%)                        | 8 (42.1)       | 2 (16.7)    | 5 (29.4) | 0.697    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 5 (26.3) | 5 (41.7) | 5 (26.3)     | 2 (16.7)    | 5 (26.3) | 5 (41.7) | 5 (26.3)     | 2 (16.7)    |
| Moderate (%)                    | 5 (26.3)       | 5 (41.7)    | 4 (23.5) | 0.697    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 5 (26.3) | 4 (41.7) | 5 (26.3)     | 2 (16.7)    | 5 (26.3) | 5 (41.7) | 5 (26.3)     | 2 (16.7)    |
| Marked (%)                      | 4 (21.1)       | 4 (33.3)    | 7 (41.2) | 0.697    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 4 (21.1) | 4 (33.3) | 4 (21.1)     | 1 (16.7)    | 4 (21.1) | 4 (33.3) | 4 (21.1)     | 1 (16.7)    |
| None (%)                        | 5 (27.8)       | 1 (8.3)     | 5 (29.4) | 0.770    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 5 (27.8) | 1 (8.3)  | 5 (27.8)     | 1 (8.3)     | 5 (27.8) | 1 (8.3)  | 5 (27.8)     | 1 (8.3)     |
| Mild (%)                        | 4 (22.2)       | 3 (25)      | 2 (11.8) | 0.770    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 4 (22.2) | 3 (25)   | 4 (22.2)     | 3 (25)      | 4 (22.2) | 3 (25)   | 4 (22.2)     | 3 (25)      |
| Moderate (%)                    | 6 (33.3)       | 5 (41.7)    | 5 (29.4) | 0.770    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 6 (33.3) | 5 (41.7) | 6 (33.3)     | 5 (41.7)    | 6 (33.3) | 5 (41.7) | 6 (33.3)     | 5 (41.7)    |
| Marked (%)                      | 3 (16.7)       | 3 (25)      | 5 (29.4) | 0.770    |            |            | 5 (62.5) | 3 (25)   | 3 (25)       | 3 (25)     | 3 (16.7) | 3 (25)   | 3 (16.7)     | 3 (25)      | 3 (16.7) | 3 (25)   | 3 (16.7)     | 3 (25)      |

Median follow-up duration, months (IQR)  

- Lauren's classification of tumor
- Antral intestinal metaplasia
- Corpus intestinal metaplasia

No number, SD standard deviation, IQR interquartile range
a. Log-rank $P = 0.004$ (N vs. E)

b. Log-rank $P = 0.001$ (N vs. E)
Log-rank $P = 0.018$ (P vs. E)
Figure 2. Cumulative incidence of metachronous cancer. (a) The cumulative incidence rate of metachronous cancer was higher in the negative group than in the eradicated group ($p = 0.004$); (b) In patients aged less than 70 years, the cumulative incidence rate of metachronous cancer development was lower in the eradicated group than in the negative and the persistent groups ($p = 0.001$ and 0.018, respectively).

$P$-values are greater than 0.05 unless otherwise stated.

Abbreviations: $N$ negative group, $E$ eradicated group, $P$ persistent group.
### Table 4. Risk factors for metachronous cancer development

| Variables                              | HR    | 95% CI      | P-value |
|----------------------------------------|-------|-------------|---------|
| Age (each incremental year)            | 1.059 | 1.001-1.120 | 0.045   |
| Male (female-reference)                | 2.827 | 0.654-12.216| 0.164   |
| Antral mucosal atrophy (each incremental grade) | 1.578 | 0.920-2.706 | 0.098   |
| Corpus mucosal atrophy (each incremental grade) | 0.790 | 0.469-1.330 | 0.375   |
| Antral intestinal metaplasia (each incremental grade) | 0.743 | 0.440-1.254 | 0.267   |
| Corpus intestinal metaplasia (each incremental grade) | 1.453 | 0.915-2.308 | 0.113   |
| Negative group (persistent group-reference) | 1.583 | 0.629-3.985 | 0.330   |
| Eradicated group (persistent group-reference) | 0.862 | 0.309-2.402 | 0.776   |

HR hazard ratio, CI confidence interval
DISCUSSION

This retrospective study aimed to investigate the long-term effect of *H. pylori* eradication on the progression of precancerous lesions to metachronous cancer after ESD for EGC. At the time of ESD, the proportion of patients with corpus mucosal in the eradicated group did not differ from that in the persistent group, and was higher than that in the negative group. This means that corpus mucosal atrophy was milder in the *H. pylori*-negative patients than the *H. pylori*-positive ones. After a mean follow-up period of 63 months, the proportion of patients with corpus mucosal atrophy in the eradicated group was lower than that in the persistent, which means *H. pylori* eradication might prevent the progression of corpus mucosal atrophy after ESD for EGC.

On the contrary, the groups did not differ significantly in the proportions of patients with antral mucosal atrophy and intestinal metaplasia. Many studies reported different results concerning the changes in precancerous lesions after *H. pylori* eradication (5-10). The most important reason for discrepant results among previous studies might be the difference in the study population. In this study, antral mucosal atrophy and intestinal metaplasia were irreversible by *H. pylori* eradication after endoscopic resection of EGC.

During the follow-up period, metachronous cancer had developed in 8.8% of patients, which did not differ significantly between the groups. In a
prospective study, *H. pylori* eradication had reduced the incidence of gastric cancer only in the subgroup without precancerous lesions (16). Another study reported that *H. pylori* eradication appeared to reduce the incidence of gastric cancer in patients without baseline precancerous gastric lesions (17). We previously reported that *H. pylori* eradication did not reduce the incidence of metachronous gastric lesions after endoscopic resection of EGC (13). These results suggested that *H. pylori* eradication might not prevent metachronous lesions in patients with precancerous lesions or cancer.

In subgroup analyses of younger patients, Kaplan–Meier analysis showed that the cumulative incidence rate of metachronous cancer development was lower in the eradicated group than in the persistent and the negative groups. The difference of metachronous cancer development in the Kaplan-Meier curves was widened at a follow-up period of 72-84 months, and continued to widen thereafter, which might indicate that *H. pylori* eradication prevents the long-term development of metachronous cancer in younger patients by delaying the progression of precancerous lesions.

Although *H. pylori* infection was reported as a risk factor of metachronous cancer development (14, 18, 19), the cumulative incidence rate of metachronous cancer was higher in the negative group than in the eradicated group for all patients and patients aged less than 70 years in this study. The mean age in the negative group was higher than in the eradicated group, and
age was an independent risk factor for metachronous cancer development in this study, which is consistent with previous studies (18, 19). The difference in age might be the reason for the higher incidence of metachronous cancer development in the negative group than in the eradicated group.

Our study had several limitations. Previous history of *H. pylori* infection and eradication before the time of ESD could not be confirmed, and the patients who had been treated for *H. pylori* infection before the time of ESD were classified as the negative group. Nonetheless, the strength of our study was the long-term follow-up of precancerous lesions as well as metachronous cancer in unified patients.

In conclusion, *H. pylori* eradication might prevent the progression of corpus mucosal atrophy, and reduce the incidence of metachronous cancer development in younger patients after endoscopic resection of EGC. Age was an independent risk factor for metachronous cancer development.
REFERENCES

1. World Health Organization. Cancer: Fact Sheet No. 297. Updated February 2015. Available at: http://www.who.int/mediacentre/factsheets/fs297/en/. Accessed March 23, 2016.

2. Chung IK, Lee JH, Lee SH, Kim SJ, Cho JY, Cho WY, et al. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. Gastrointestinal endoscopy. 2009;69(7):1228-35.

3. Isomoto H, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, et al. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. Gut. 2009;58(3):331-6.

4. Correa P, Houghton J. Carcinogenesis of Helicobacter pylori. Gastroenterology. 2007;133(2):659-72.

5. Rokkas T, Pistiolas D, Sechopoulos P, Robotis I, Margantinis G. The long-term impact of Helicobacter pylori eradication on gastric histology: a systematic review and meta-analysis. Helicobacter. 2007;12 Suppl 2:32-8.

6. Wang J, Xu L, Shi R, Huang X, Li SW, Huang Z, et al. Gastric
atrophy and intestinal metaplasia before and after Helicobacter pylori eradication: a meta-analysis. Digestion. 2011;83(4):253-60.

7. Toyokawa T, Suwaki K, Miyake Y, Nakatsu M, Ando M. Eradication of Helicobacter pylori infection improved gastric mucosal atrophy and prevented progression of intestinal metaplasia, especially in the elderly population: a long-term prospective cohort study. Journal of gastroenterology and hepatology. 2010;25(3):544-7.

8. Ito M, Haruma K, Kamada T, Mihara M, Kim S, Kitadai Y, et al. Helicobacter pylori eradication therapy improves atrophic gastritis and intestinal metaplasia: a 5-year prospective study of patients with atrophic gastritis. Alimentary pharmacology & therapeutics. 2002;16(8):1449-56.

9. Kong YJ, Yi HG, Dai JC, Wei MX. Histological changes of gastric mucosa after Helicobacter pylori eradication: a systematic review and meta-analysis. World journal of gastroenterology. 2014;20(19):5903-11.

10. Ohkusa T, Fujiki K, Takashimizu I, Kumagai J, Tanizawa T, Eishi Y, et al. Improvement in atrophic gastritis and intestinal metaplasia in patients in whom Helicobacter pylori was eradicated. Annals of internal medicine. 2001;134(5):380-6.

11. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous
gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. Lancet (London, England). 2008;372(9636):392-7.

12. Yoon SB, Park JM, Lim CH, Cho YK, Choi MG. Effect of Helicobacter pylori eradication on metachronous gastric cancer after endoscopic resection of gastric tumors: a meta-analysis. Helicobacter. 2014;19(4):243-8.

13. Choi J, Kim SG, Yoon H, Im JP, Kim JS, Kim WH, et al. Eradication of Helicobacter pylori after endoscopic resection of gastric tumors does not reduce incidence of metachronous gastric carcinoma. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 2014;12(5):793-800.e1.

14. Jung S, Park CH, Kim EH, Shin SJ, Chung H, Lee H, et al. Preventing metachronous gastric lesions after endoscopic submucosal dissection through Helicobacter pylori eradication. Journal of gastroenterology and hepatology. 2015;30(1):75-81.

15. Japanese classification of gastric carcinoma: 3rd English edition. Gastric cancer: official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association. 2011;14(2):101-12.

16. Wong BC, Lam SK, Wong WM, Chen JS, Zheng TT, Feng RE, et al.
Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. Journal of the American Medical Association. 2004;291(2):187-94.

17. Fuccio L, Zagari RM, Minardi ME, Bazzoli F. Systematic review: Helicobacter pylori eradication for the prevention of gastric cancer. Alimentary pharmacology & therapeutics. 2007;25(2):133-41.

18. Kim YI, Choi IJ, Kook MC, Cho SJ, Lee JY, Kim CG, et al. The association between Helicobacter pylori status and incidence of metachronous gastric cancer after endoscopic resection of early gastric cancer. Helicobacter. 2014;19(3):194-201.

19. Kwon YH, Heo J, Lee HS, Cho CM, Jeon SW. Failure of Helicobacter pylori eradication and age are independent risk factors for recurrent neoplasia after endoscopic resection of early gastric cancer in 283 patients. Alimentary pharmacology & therapeutics. 2014;39(6):609-18.
한글 초록

서론: HELICOBACTER PYLORI 감염에 의한 위축성 위염과 장상피화생은 위암의 주요한 전암성 병변이다. 조기위암의 내시경 절제술 후에 HELICOBACTER PYLORI 제균치료를 하는 것이 전암성 병변의 진행과 후시성 위암의 발생에 어떠한 장기적인 영향을 미치는지 알아보고 자 이 연구를 진행하였다.

방법: 조기위암으로 내시경 절제술을 받은 환자들의 의무기록을 후향적으로 분석하였다. 전암성 병변의 변화와 후시성 위암의 발생을 HELICOBACTER PYLORI 감염 및 제균 여부에 따라 군을 나누어 비교하였다.

결과: 총 565명의 환자를 평균 5년 이상의 기간동안 추적관찰하였다. 체부의 위축성 위염의 정도는 관찰 기간 동안 감염군보다 제균군에서 유의하게 낮아졌다 ($p = 0.015$). 70세 미만의 환자들중에서 후시성 위암의 누적발생률은 감염군보다 제균군에서 더 낮았다 ($p = 0.018$). 나이가 후시성 위암 발생의 독립적인 위험인자였다.

결론: HELICOBACTER PYLORI 제균은 젊은 환자에게 있어서 전암성 병변의 진행을 늦출 것으로서 후시성 위암이 발생을 장기적으로 낮출 수 있다.
주요어: 헬리코박터 파일로리, 제균, 위암, 위축, 장상피화생
학번: 2015-22266