Effect of *Helicobacter pylori* Eradication on Metachronous Recurrence After Endoscopic Resection of Gastric Neoplasm

Suh Eun Bae, MD[1], Hwoon-Yong Jung, MD, PhD, AGAF[1], June Kang, MD[2], Young Soo Park, MD, PhD[2], Seunghee Baek, PhD[3], Ji-Hoon Jung, MD[1], Ji Young Choi, MD[1], Mi-Young Kim, MD[1], Ji Yong Ahn, MD[1], Kwi-Sook Choi, MD[1], Do Hoon Kim, MD[1], Jeong Hoon Lee, MD[1], Kee Don Choi, MD, PhD[1], Ho June Song, MD, PhD[1], Gin Hyug Lee, MD, PhD[1] and Jin-Ho Kim, MD, PhD[1]

OBJECTIVES: **Although many epidemiologic studies have shown that *Helicobacter pylori* (*H. pylori*) eradication has prophylactic effects on gastric cancer, their results are less clear in high-risk populations. We conducted this study to examine whether *H. pylori* eradication would affect the occurrence of metachronous gastric cancer after endoscopic resection in patients with early gastric cancer.**

METHODS: **We retrospectively analyzed 2,089 adults who underwent endoscopic resection of gastric low-grade neoplasia, high-grade neoplasia, or differentiated invasive neoplasia from 2004 to 2008 at Asan Medical Center. Of these, a total of 1,007 patients with early gastric cancer were enrolled in this study. We evaluated the demographic data, the pathology, and the incidence of metachronous recurrence by dividing them into three groups: those without active *H. pylori* infection (Hp negative group, $n=340$), those who successfully underwent *H. pylori* eradication (eradicated group, $n=485$), and those who failed or did not undergo *H. pylori* eradication (noneradicated group, $n=182$).**

RESULTS: **Metachronous recurrence was diagnosed in 75 patients, including 17 in the Hp, 34 in the eradicated, and 24 in the noneradicated groups. Median time to metachronous recurrence was 18 months (range, 7–75 months). The incidence of metachronous gastric cancer was 10.9 cases per 1,000 person-years in the Hp negative group, 14.7 cases per 1,000 person-years in the eradicated group, and 29.7 cases per 1,000 person-years in the noneradicated group. The hazard ratios in the noneradicated group compared with the Hp negative and eradicated groups were 2.5 ($P<0.01$) and 1.9 ($P=0.02$), respectively. *H. pylori* eradication reduced metachronous recurrence of gastric neoplasm, which was also shown in the secondary analysis of 1,487 patients with low-grade neoplasia and early gastric cancer.**

CONCLUSIONS: **Successful *H. pylori* eradication may reduce the occurrence of metachronous gastric cancer after endoscopic resection in patients with early gastric cancer.**

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is the most important risk factor for gastric adenocarcinoma (1–5). The mucosa infected by *H. pylori* progresses through the stages of chronic active gastritis, atrophy, intestinal metaplasia, and dysplasia, followed by the development of gastric adenocarcinoma. In 1994, the International Agency for Research on Cancer (IARC), a subsidiary of the World Health Organization (WHO), categorized *H. pylori* as a group 1 carcinogen for gastric cancer (6).

Although many epidemiologic studies have shown that *H. pylori* eradication has prophylactic effects on gastric cancer, their results are less clear in high-risk populations (7–10). According to a large-scale, double-blinded, randomized study conducted in China, although *H. pylori* eradication significantly decreased the

[1]Department of Gastroenterology, University of Ulsan College of Medicine, Asan Medical Center, Asan Digestive Disease Research Institute, Seoul, South Korea; [2]Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, Asan Digestive Disease Research Institute, Seoul, South Korea; [3]Department of Clinical Epidemiology and Biostatistics, University of Ulsan College of Medicine, Asan Medical Center, Asan Digestive Disease Research Institute, Seoul, South Korea. **Correspondence:** Hwoon-Yong Jung, MD, PhD, AGAF, Department of Gastroenterology, University of Ulsan College of Medicine, Asan Medical Center, Asan Digestive Disease Research Institute, 388-1 Pungnap-dong Songpa-gu, 138-736 Seoul, South Korea. E-mail: hyjung@amc.seoul.kr
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development of gastric cancer in low-risk populations, it had no effects on the incidence of gastric cancer in high-risk populations (10). In this study, *H. pylori* eradication was an effective modality in the total enrolled patients during a follow-up period of 15 years. However, 59.4% of them had chronic active gastritis. Moreover, it did not analyze a high-risk group of patients (11). However, according to an open-label, randomized controlled study conducted in Japan, *H. pylori* eradication after endoscopic resection of early gastric cancer prevented the occurrence of metachronous gastric cancer (12).

In Korea, endoscopic resection is commonly performed for patients with noninvasive low-grade neoplasia with risk factors (depressed morphology, surface erythema, or a size ≥1 cm), noninvasive high-grade neoplasia, and differentiated invasive neoplasia (intramucosal carcinoma and superficial submucosal carcinoma with submucosal invasion within 500 μm) in the stomach based on the new Vienna classification for histological diagnosis (13,14). Through our extensive experience in endoscopic resection, we observed that *H. pylori* eradication tended to reduce the metachronous recurrence of gastric neoplasms in patients who underwent endoscopic resection of gastric neoplasms, including those with low-grade neoplasia. Given the above background, we conducted this study to examine whether *H. pylori* eradication would affect the occurrence of metachronous gastric cancer after endoscopic resection in patients with early gastric cancer.

METHODS

Patients

Between November 2004 and December 2008, 2,089 patients underwent endoscopic resection of gastric low-grade neoplasia, high-grade neoplasia, and differentiated invasive neoplasia at Asan Medical Center, Seoul, Korea. Of these patients, we excluded 382 patients with follow-up period of <2 years. We also excluded 220 patients who had not undergone tests for active *H. pylori* infection (e.g., urea breath tests, rapid urease tests, and histopathologic examination) at the time of endoscopy. Furthermore, we also excluded 480 patients who had been diagnosed with low-grade neoplasia, but included those with early gastric cancer corresponding to categories 4 and 5 based on the Vienna classification.

We therefore enrolled a total of 1,007 patients with early gastric cancer in this study. Our clinical series of patients comprised 785 men (78.0%) with a median age of 63 years (range, 28–88 years). In addition, there were 525 smokers (52.1%) and 574 drinkers (57.0%). Our clinical series of patients were followed-up during a median period of 60 months (range, 24–137 months). In addition, there was a 1-month median interval (range, 0–12 months) between endoscopic resection and *H. pylori* eradication.

As shown in **Figure 1**, depending on the presence of active *H. pylori* infection or successful *H. pylori* eradication, the patients were divided into three groups: (i) those without active *H. pylori* infection at the time of resection (Hp negative group, $n=340$, 33.8%); (ii) those who successfully underwent *H. pylori* eradication (eradicated group, $n=485$, 48.2%); and (iii) those who failed or did not undergo *H. pylori* eradication (noneradicated group, $n=182$, 18.1%).

The patients of the eradicated group received lansoprazole 30 mg or pantoplazole 40 mg or omeprazole 30 mg twice daily, amoxicillin 750 mg twice daily, and clarithromycin 200 mg twice daily for 7–14 days.

Serological status of the Hp negative group

All the patients ($n=340$) in the Hp negative group were *H. pylori* negative on histopathologic examinations of the resected specimen, urea breath tests, and/or rapid urease tests. The serologic

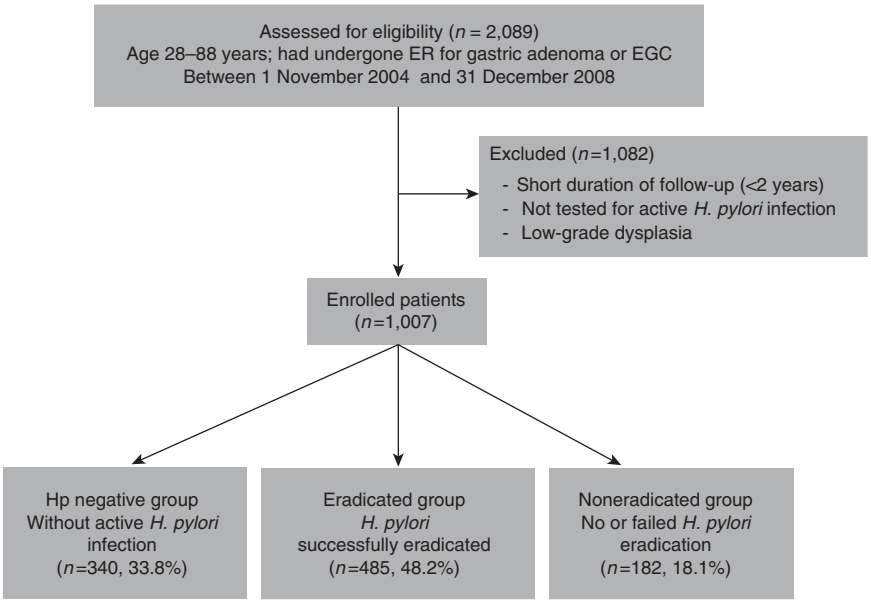

Figure 1. Patient flow diagram. EGC, early gastric cancer; ER, endoscopic resection; Hp, *Helicobacter pylori*.

test used for the serology in the Hp group was IMMULITE 2000 *H. pylori* IgG produced by SIEMENS (Siemens Healthcare Diagnostics Products Ltd. Llanberis, Gwynedd, UK) and a qualitative chemiluminescent immunometric assay. *H. pylori* serologic status was available for 240 of the 340 patients (71.6%); of these 240, 72 (21.2%) were serologically positive (> 1.5 U/ml), 144 (42.4%) were serologically negative (< 0.9 U/ml), and 24 (7.1%) were serologically equivocal (0.8–1.5 U/ml). Information about *H. pylori* serologic status was not available for the other 100 patients (29.4%).

Follow-up schedule

In all the specimens of endoscopic resection, sampled from the patients who underwent endoscopic resection of gastric neoplasm, we reviewed the lateral and vertical margin and lymphovascular invasion. Moreover, we considered surgery in the patients who had lesions of submucosal invasion of more than 500 μm or those with a positive lymphovascular invasion. Patients with residual neoplasms, however, were not enrolled in this study. The patients underwent endoscopic resection of early gastric cancer and then were followed-up with endoscopy by forceps biopsy and/or computed tomography scan at 3, 6, 12, 18, and 24 months, and a 1-year interval thereafter.

Histopathologic examinations

We reviewed endoscopically resected specimens to examine whether the patients were accurately diagnosed with early gastric cancer on histopathologic examinations and to evaluate the status of gastric mucosa in the noncancerous regions that are at least 1 cm distal to the tumor margin. To do this, we graded the gastric atrophy and intestinal metaplasia into "None," "Mild," "Moderate," and "Severe" based on the modified Sydney classification (Houston) (15).

Outcome measures

In this study, the rate of metachronous recurrence of gastric cancer at follow-up in 1,007 patients served as the primary outcome measure. In addition, the rate of metachronous recurrence of gastric neoplasm at follow-up in 1,487 patients with gastric low-grade neoplasia and early gastric cancer served as the secondary outcome measure. We excluded metachronous recurrence occurring within 6 months because the lesions detection at this time would most likely be due to those missed before, and should be categorized as synchronous cancers or neoplasms.

Statistical analysis

The demographic data of the three groups and their rates of metachronous recurrence were compared using χ^2 tests. Continuous variables, including age, the maximum diameter of lesions, and the interval between endoscopic resection and *H. pylori* eradication, and the median follow-up period and recurrence rate between three groups were compared using analysis of variance tests. Recurrence-free survival was calculated using the Kaplan–Meier method. Risk factors for recurrence-free survival, including sex, age, smoking, alcohol, histology, the maximum diameter of the lesion, the depth of invasion, and the median follow-up period, were evaluated using Cox proportional hazard models. Because there was no metachronous recurrence in all patients without atrophy or metaplasia, we did not analyze the correlations of atrophy and metaplasia with recurrence-free survival using Cox proportional hazard model. Statistical analysis was done using the SAS statistical software, version 8.2 (SAS Institute, Cary, NC). A two-tailed P value of < 0.05 was considered statistically significant.

RESULTS

Histopathologic findings

Endoscopically resected specimens were available from 792 of the 1,007 patients (78.6%). Of these 792 patients, 786 (99.2%) had atrophy and 778 (98.2%) had metaplasia in the adjacent background mucosa. Of the 786 patients with atrophy, 2.5% had mild, 1.2% had moderate, and 95.2% had severe atrophy. Of the 778 patients with metaplasia, 1.5% had mild, 1.3% had moderate, and 95.0% had severe metaplasia. The incidence of atrophy and metaplasia was significantly lower in the Hp negative group as compared with the eradicated and noneradicated groups. Of the 1,007 patients, 992 (98.5%) had intestinal-type and 15 (1.5%) had diffuse-type early gastric cancer. Of the 15 patients with diffuse-type early gastric cancer, 6 were in the Hp negative group, 6 in the eradicated group, and 3 in the noneradicated group. Of the 1,007 enrolled patients, 921 (91.5%) had mucosal cancer. The median maximum diameter of lesion was 1.8 cm (range, 0.2–12.1 cm) and 1.5 cm (range, 0.2–9.8 cm) in the Hp negative group, 1.8 cm (range, 0.2–12.1 cm) in the eradicated group, and 2.0 cm (range, 0.6–9.8 cm) in the noneradicated group, with significant differences among these three groups (**Table 1**).

Metachronous recurrence

Overall, the incidence of metachronous cancer was 16.0 cases per 1,000 person-years during a median period of 60 months (range, 24–137 months). The median time to recurrence was 18 months (range, 7–75 months). Rates of metachronous cancer in the Hp negative, eradicated, and noneradicated groups were 10.9, 14.7, and 29.7 cases per 1,000 person-years (**Table 2**). There were no significant differences in the recurrence rate and recurrence-free survival between the Hp negative and eradicated groups, but the recurrence rate was significantly higher in the noneradicated than in the Hp negative and eradicated groups.

Moreover, we also analyzed the patients again after excluding those who had a metachronous recurrence within a 1-year period. Of the 75 patients with metachronous recurrence, 21 experienced recurrence within the 1-year period. The incidence of metachronous cancer was 11.3 cases per 1,000 person-years during a median period of 60 months (range, 24–137 months). In addition, it was 8.9 cases per 1,000 person-years in the Hp negative group, 9.3 cases per 1,000 person-years in the eradicated group, and 21.4 cases per 1,000 person-years in the noneradicated group. There were no significant differences in the recurrence rate and recurrence-free survival between the Hp negative and eradicated groups. However, the recurrence rate was significantly higher in the noneradicated as compared with the Hp negative and eradicated groups.

Table 1. Baseline characteristics of the enrolled patients

	Hp negative group (*N*=340)	Eradicated group (*N*=485)	Noneradicated group (*N*=182)	*P* value
Median age, years (range)	63 (33–88)	62 (28–84)	64 (36–83)	0.01[a]
Sex				0.67
Male (%)	260 (77)	380 (78)	145 (80)	
Female (%)	80 (24)	105 (22)	37 (20)	
Smoking (%)	49.7	53.6	52.7	0.53
Alcohol (%)	57.4	58.4	52.7	0.42
Histology				0.81
Intestinal type (%)	334 (98.2)	479 (98.8)	179 (98.4)	
Diffuse type (%)	6 (1.8)	6 (1.2)	3 (1.6)	
Depth of invasion				0.17
Mucosa (%)	314 (92.4)	447 (92.2)	160 (87.9)	
Submucosa (%)	26 (7.6)	38 (7.8)	22 (12.1)	
Maximum diameter of lesion (cm)	1.5 (0.2–9.8)	1.8 (0.2–12.1)	2.0 (0.6–9.8)	<0.01[b]
Atrophy (%)	97.5	99.8	99.6	<0.01[b]
Metaplasia (%)	96.1	98.8	99.1	<0.01[b]

Hp, *Helicobacter pylori*.
[a]Hp negative, noneradicated group vs. eradicated group:
[b]Hp negative vs. eradicated group, noneradicated group.
There was a significant difference in age among the three groups. The maximum diameter of lesion and the degree of atrophy and metaplasia were significantly smaller and lower in the Hp negative group as compared with the eradicated and noneradicated groups.

Table 2. Metachronous recurrence rate and duration of follow-up in the three groups

	Hp negative group	Eradicated group	Noneradicated group	*P* value
Median duration of follow-up, months (range)	59.0 (24–116)	59 (24–137)	61.5 (24–114)	0.30
Metachronous recurrence rate, cases per 1,000 person-years (%)	10.9 (5.0)	14.7 (7.0)	29.7 (13.2)	<0.01[a]
Median duration of recurrence, months				
Since endoscopic resection (range)	24.0 (5–66)	22.0 (7–75)	16.0 (6–63)	0.15
Since eradication of *H. pylori* (range)		15.0 (1–71)	16.0 (6–63)	0.44

Hp, *Helicobacter pylori*.
[a]Hp negative, eradicated group vs. noneradicated group.
There were no significant differences in the recurrence rate (10.9 vs. 14.7, *P*=0.24) and recurrence-free survival between the Hp negative and eradicated groups. But the recurrence rate was significantly higher in the noneradicated group as compared with the Hp negative group (29.7 vs. 10.9, *P*<0.01) and the eradicated group (29.7 vs. 14.7, *P*=0.01).

The cumulative recurrence-free survival was significantly lower in the noneradicated group at a follow-up since the time of endoscopic resection as well as the confirmation of *H. pylori* eradication (**Figure 2a,b**). Similar findings were observed after excluding patients who experienced metachronous recurrence within 1 year. Univariate analysis showed that the risk of metachronous recurrence was higher in the noneradicated than in the Hp negative (hazard ratio (HR) 2.7) and eradicated (HR 2.0) groups. Similarly, multivariate analysis showed that the risk of metachronous recurrence was higher in the noneradicated than in the Hp negative (HR 2.5) and eradicated (HR 1.9) groups (**Table 3**).

Interval to metachronous recurrence

The median time to recurrence was 18 months (range, 7–75 months). Of the 75 patients with metachronous recurrence, 21 experienced recurrences within 1 year. Of these 75 patients, 4 patients, including 2 in the Hp negative group and 1 each in the eradicated and noneradicated groups, had more than two recurrences times. Metachronous recurrence tended to occur within 2 years in the eradicated group, including 18 within 2 years and 16 after 2 years, whereas it occurred later in the Hp negative and noneradicated groups (**Figure 2a,b**).

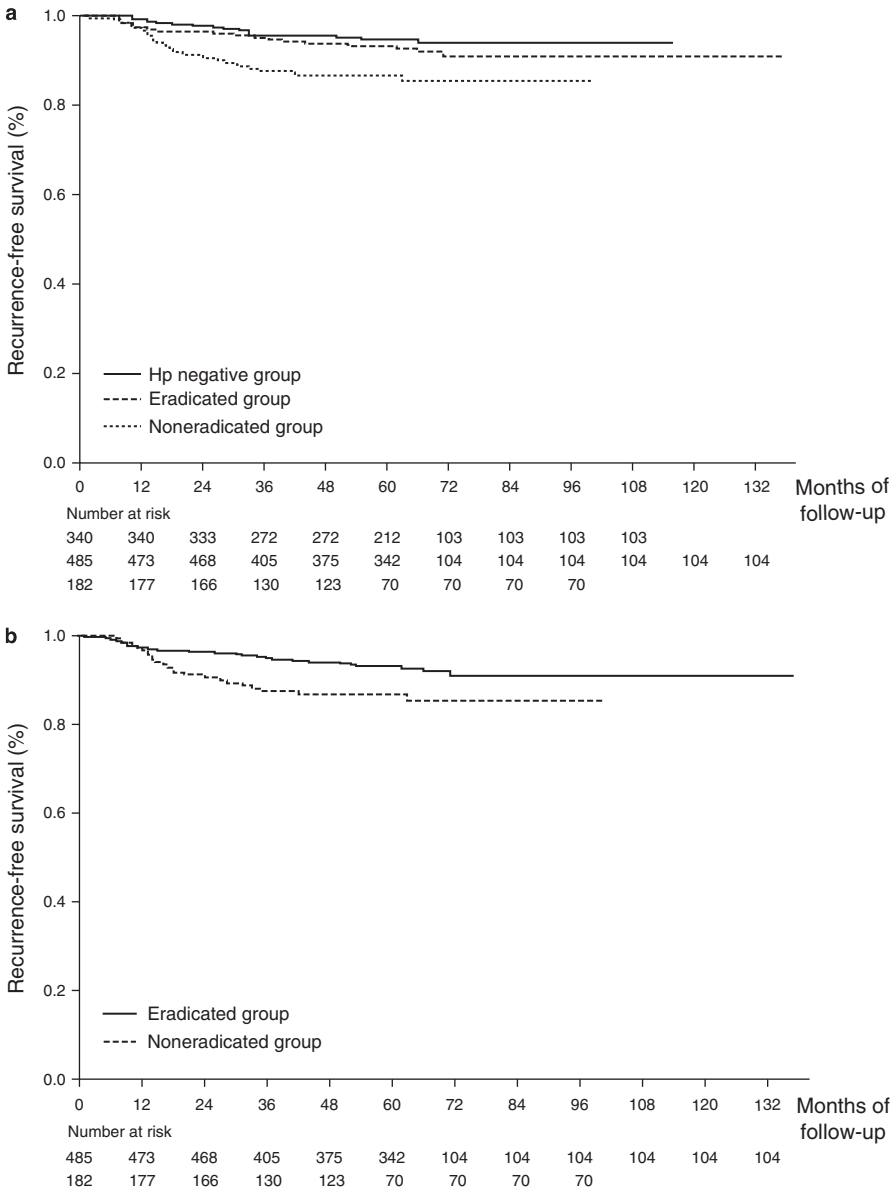

Figure 2. Kaplan–Meier analysis of recurrence-free survival. (**a**) Follow-up after endoscopic resection and (**b**) follow-up after determination of *Helicobacter pylori* status after eradication. The cumulative recurrence-free survival was significantly lower in the noneradicated group at follow-up since the time of endoscopic resection as well as the confirmation of *H. pylori* eradication.

Table 3. Univariate and multivariate Cox proportional hazards model for recurrence-free survival

		Univariate analysis		Multivariate analysis	
Dependent variables		**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Noneradicated group	vs. Hp negative group	2.7 (1.47–5.09)	<0.01	2.5 (1.35–4.77)	<0.01
	vs. eradicated group	2.0 (1.18–3.34)	0.01	1.9 (1.09–3.18)	0.02

CI, confidence interval; Hp, *Helicobacter pylori*; HR, hazard ratio.

Univariate analysis showed that the risk of metachronous recurrence was higher in the noneradicated group than in the Hp negative group (HR 2.7) and the eradicated group (HR 2.0). Multivariate analysis also showed that recurrence-free survival was lower in the noneradicated group than in the Hp negative (HR 2.5) and eradicated (HR 1.9) groups.

Table 4. Univariate and multivariate Cox proportional hazards model for recurrence-free survival in patients with gastric low-grade neoplasia and early gastric cancer

Dependent variables		Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Noneradicated group	vs. Hp negative group	3.7 (2.33–5.98)	<0.01	3.6 (2.22–5.74)	<0.01
	vs. eradicated group	2.9 (1.90–4.39)	<0.01	2.8 (1.83–4.28)	<0.01
Male gender vs. female		2.3 (1.29–3.95)	<0.01	2.0 (1.04–3.74)	0.04
Smoking		1.5 (1.03–2.16)	0.03		

CI, confidence interval; Hp, *Helicobacter pylori*; HR, hazard ratio.

Univariate analysis showed that risk of metachronous recurrence was higher in the noneradicated group than in the Hp negative (HR 3.7) and the eradicated (HR 2.9) groups. Multivariate analysis showed that factors significantly affecting recurrence-free survival were noneradication of *H. pylori* status and male gender, and that recurrence-free survival was lower in the noneradicated group than in the Hp negative (HR 3.6) and eradicated (HR 2.8) groups.

Assessment of secondary outcome measure

Finally, we also included 480 patients with low-grade neoplasia in this analysis. Of the 2,089 patients who underwent endoscopic resection of gastric neoplasms, a total of 1,487 patients, corresponding to categories 3, 4, and 5 on the Vienna classification, were analyzed. Recurrence-free survival patterns in these 1,487 patients showed the same pattern as the 1,007 patients with early gastric cancer. Multivariate analysis showed that the risk of metachronous recurrence was significantly higher in the noneradicated than in the Hp negative group (HR 3.6) and eradicated group (HR 2.8; $P<0.01$; **Table 4**). Similarly, metachronous recurrence after successful *H. pylori* eradication tended to occur within 2 years in the eradicated group, including 39 within 2 years and 14 after 2 years, whereas it occurred later in the Hp negative group and noneradicated group. The median time to metachronous recurrence was significantly shorter in the eradicated group (10.0 months) than in either the Hp negative group (28.0 months) or the noneradicated group (18.0 months).

DISCUSSION

In Korea, endoscopic resection is a mainstream modality in patients with intramucosal gastric cancer with differentiated histology that is based on many Korean and Japanese reports that there is no significant difference in long-term survival between endoscopic resection and surgery for intramucosal gastric cancer (16–19). It is our treatment policy in patients with gastric neoplasm to monitor the clinical course of low-grade neoplasia without risk factors and to perform active removal of low-grade neoplasia with gross features of malignancy or over 1 cm in size, and early gastric cancer of categories 4 and 5 based on the Vienna classification (14).

Even after endoscopic resection, nearly all the abnormal gastric mucosa tissues are left. This often leads to metachronous occurrence of gastric neoplasms in the background stomach. The risk of metachronous gastric cancer may be related to the severity of atrophy and metaplasia in the background stomach, and to the size of the remaining mucosa. One study in Korea showed that patients who underwent endoscopic mucosal resection were at higher risk of metachronous gastric cancers than those who underwent surgery (HR 6.7; 95% confidence interval, 2.00–22.58) (16). In that study, however, all metachronous gastric cancers occurring after endoscopic mucosal resection were successfully retreated, without affecting overall survival.

Many controversies exist regarding whether *H. pylori* eradication would be effective in preventing the occurrence of gastric cancer in patients with atrophy and metaplasia. To date, its efficacy has been contradicted in many studies, but has been advocated in some studies. Several prospective, randomized clinical studies have been conducted to evaluate it in Japan and China (10–12,20,21). Of these, a randomized, interventional, controlled study was conducted in a high-risk region of China that showed that its efficacy did not reach statistical significance in a high-risk group of patients (10). Moreover, *H. pylori* eradication in a subgroup of infected patients without precancerous lesions significantly decreased the development of gastric cancer, suggesting that eradication of *H. pylori* before changes occur in the gastric mucosa may be very important in preventing the development of gastric cancer. According to another study conducted in China, *H. pylori* eradication significantly reduced the occurrence of gastric cancer in patients who are at decreased risks at baseline risks (e.g., those without atrophy) (22). According to a randomized, interventional, controlled study conducted in 795 patients from Colombia, there were a total of 9 patients (5 of the eradicated group and 4 of the control group) who developed gastric cancer at a 12-year follow-up, all of whom had intestinal metaplasia and/or dysplasia. These results indicate that *H. pylori* eradication did not reduce the incidence of gastric cancer in patients who had intestinal metaplasia and/or dysplasia at baseline (23). This study was a population-based study where the authors did not evaluate the efficacy of *H. pylori* eradication for the prevention of metachronous recurrence.

According to many Japanese reports, however, *H. pylori* eradication reduced the incidence of gastric cancer in high-risk patients (12,21,24,25). Of these, a nonrandomized clinical study was conducted in 944 patients of the *H. pylori* eradication group and 176 of the non-*H. pylori* eradication group who were followed-up endoscopically during a period for 3.4 years, thus suggesting that *H. pylori* eradication prevented the occurrence of gastric cancer (24). Moreover, a randomized, prospective clinical study was conducted in 544 patients from Japan, where the early gastric

cancer was endoscopically resected, thus showing that prophylactic *H. pylori* eradication after endoscopic resection significantly decreased the incidence of metachronous gastric cancer (12). In this study, the incidence of metachronous gastric cancer was 14.1 cases per 1,000 person-years in *H. pylori* eradication group and 40.5 cases per 1,000 person-years in the non-*H. pylori* eradication group during a median follow-up period of 1,076 days. Several reports about the metachronous recurrence of gastric cancer have also shown positive results.

This study is the largest retrospective cohort study. Our results showed that the rate of metachronous recurrence was significantly lower (14.7 cases per 1,000 person-years in the eradicated group and 29.7 cases per 1,000 person-years in the noneradicated group, HR 1.9) that is consistent with a prospective, randomized study (12). Of the total enrolled patients, 95% had severe atrophy and severe metaplasia in the adjacent mucosa. This suggests that *H. pylori* eradication had a preventive effect against metachronous gastric cancer in high-risk patients with active *H. pylori* infection. Based on our results, it can be inferred that *H. pylori* eradication might be effective in preventing the metachronous recurrence despite the presence of severe atrophy and metaplasia in the adjacent mucosa in patients with active *H. pylori* infections. Moreover, our results also showed that *H. pylori* eradication reduced metachronous recurrence of gastric neoplasms in 1,487 patients with low-grade neoplasia or early gastric cancer.

In our series, metachronous recurrence occurred within 2 years of *H. pylori* eradication in the Hp negative group as compared with the eradicated group and the noneradicated group. This was also shown in the secondary analysis of 1,487 patients with gastric low-grade neoplasia and early gastric cancer. We commonly perform endoscopic resection for patients with noninvasive low-grade neoplasia with risk factors (depressed morphology, surface erythema, or a tumor size ≥1 cm). We therefore assume that the results of the secondary analysis are of greater clinical significance. Presumably, this might be because microcarcinomas or precancerous lesions (such as low-grade dysplasia) often arise coincidentally at the time of endoscopic resection. More importantly, *H. pylori* eradication could lower the possibility that gastric atrophy and metaplasia might progress to the gastric cancer. In addition, it may take several years for new gastric cancer to occur. This is similar to the effects of smoking cessation for the prevention of lung cancer. Individuals who quit smoking are at increased risks of developing lung cancer for less than 1–2 years. After certain periods of time since smoking cessation, however, the risk of developing lung cancer is significantly reduced over time (26,27).

We reviewed the serologic status of *H. pylori* infection in the Hp negative group. Information about *H. pylori* serologic status was available for 240 of the total 340 patients, with 72 patients being serologically positive, 144 being serologically negative, and 24 being serologically equivocal. Recurrence rates between patients being serologically positive vs. patients being serologically negative were not significant differences (6 among 72 patients vs. 12 among 144 patients, $P=0.39$).

Although *H. pylori* IgG serology tends to be decreased after eradication, a portion of the patients could still remain seropositive after many years (28). The patients in the Hp negative group are quite heterogeneous, consisting of at least three types: (i) patients with chronic *H. pylori* infection that is no longer manifested histologically due to severe gastric atrophy and intestinal metaplasia; (ii) patients who once underwent *H. pylori* eradication and remain negative for *H. pylori* infection, and (iii) patients never infected with *H. pylori*. We assume that patients (i) are at increased risks of developing gastric cancer as compared with the eradicated group and the patients (ii) or (iii) are at decreased risks of developing gastric cancer as compared with the eradicated group. This is because longer periods of time elapsed since they underwent *H. pylori* eradication. This led to the speculation that there is no significant difference in the degree of risk of development gastric cancer between the Hp group and the eradicated group.

In this study, there were significant differences in baseline characteristics, such as age, the maximum diameter of lesion, atrophy, and metaplasia, among the three groups. On the Cox proportional hazard model, however, there was no significant correlation between the rate of metachronous recurrence and the baseline characteristics.

There are two limitations of this as shown below. First, this study is a retrospective cohort analysis. However, we reviewed the resected specimens that had been prospectively collected from 78.6% of total patients. This may in part reduce the limitations of retrospective setting. Second, we used endoscopically resected specimens to analyze the degree of atrophy and metaplasia. We could not therefore examine the degree of atrophy and metaplasia in the whole stomach. The status of the adjacent mucosa is not indicative of the whole stomach. In addition, there was no metachronous recurrence in all patients without atrophy or metaplasia. We could not therefore analyze the effects of atrophy and metaplasia on the rate of metachronous recurrence in the Cox proportional hazard model. However, pathological review may be important in defining the status of the adjacent mucosa, which is based on the consideration that gastric cancer occurred in the mucosa with severe atrophy and metaplasia. Furthermore, the presence of *H. pylori* at the time of endoscopic resection may indicate less-severe atrophy or intestinal metaplasia.

To summarize, our results showed that *H. pylori* eradication significantly reduced metachronous recurrence of gastric cancer in high-risk patients with a history of endoscopic resection of gastric cancer in the background of atrophy and metaplasia. However, our results may be limited to high-risk individuals and cannot be applied to patients without risk factors of gastric cancer (e.g., absence of atrophy/metaplasia, or a lack of past history of gastric cancer). Taken together, however, our results suggest that there is a causal relationship between *H. pylori* infection and gastric cancer. It can therefore be concluded that clinicians should consider using *H. pylori* eradication for the prevention of metachronous recurrence of gastric cancer in high-risk patients.

CONFLICT OF INTEREST

Guarantor of the article: Hwoon-Yong Jung, MD, PhD, AGAF.
Specific author contributions: Hwoon-Yong Jung: study planning and study coordination; Suh Eun Bae: data collection, study coordination,

and manuscript drafting; Suh Eun Bae, June Kang, and Young-Su Park: histopathology examination; Seunghee Baek: data analysis and interpretation; Ji-Hoon Jung, Ji Young Choi, Mi-Young Kim, Ji-Yong Ahn, Kwi-Sook Choi, Do Hoon Kim, Jeong Hoon Lee, Kee Don Choi, Ho June Song, Gin Hyug Lee, and Jin-Ho Kim: study planning and reviews. All authors have read and approved the submitted version of the paper.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ *Helicobacter pylori* infection is the most important risk factor for gastric adenocarcinoma.
- ✓ Although many epidemiologic studies have shown that *H. pylori* eradication has prophylactic effects on gastric cancer, their results are less clear in high-risk populations.
- ✓ In Korea, endoscopic resection is commonly performed for patients with noninvasive low-grade neoplasia with risk factors (e.g., depressed morphology, surface erythema, or size ≥1 cm), noninvasive high-grade neoplasia, and differentiated invasive neoplasia (intramucosal carcinoma or superficial submucosal carcinoma (submucosal invasion within 500 μm)) in the stomach, based on the new Vienna classification for histological diagnosis.

WHAT IS NEW HERE

- ✓ We found that metachronous recurrence rate was significantly lower in patients who underwent successful *H. pylori* eradication than in patients with failed or no *H. pylori* eradication (14.7 vs. 29.7 cases per 1,000 person-years, hazard ratio (HR) 2.5).
- ✓ Of the total enrolled patients, 95% had severe atrophy and severe metaplasia in the adjacent mucosa. This suggests that *H. pylori* eradication had a preventive effect against metachronous gastric cancer in high-risk patients with active *H. pylori* infection.
- ✓ We reviewed endoscopically resected specimens to examine whether the patients were accurately diagnosed with early gastric cancer on histopathologic examinations and to evaluate the status of gastric mucosa in the noncancerous regions that are at least 1 cm distal to the tumor margin. *H. pylori* eradication reduced metachronous recurrence of gastric neoplasms, which was also shown in the secondary analysis of 1,487 patients with low-grade neoplasia or early gastric cancer.

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