



Risk Factors for Metachronous Recurrence after Endoscopic Submucosal Dissection of Early Gastric Cancer

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Although endoscopic submucosal dissection (ESD) is widely accepted as a curative treatment method for early gastric cancer (EGC) worldwide, metachronous recurrence often occurs after ESD for EGC. However, there are insufficient data about the role of *Helicobacter pylori* (*H. pylori*) infection and other risk factors for recurrence. We aimed to compare the metachronous lesion in the *H. pylori* persistent group and the eradicated group, and to identify risk factors for metachronous lesion. We retrospectively analyzed 782 patients who underwent ESD between January 2008 and December 2013. We excluded patients with dysplasia or patients who were not tested for *H. pylori* infection. One hundred eighty-five patients were enrolled. We studied risk factors for recurrence, and used survival analysis to test. There were 24 patients with metachronous recurrence after ESD for EGC among the group. The incidence of metachronous gastric lesions after ESD for EGC developed more in the over 70-year-old group ($P = 0.025$) and more in the *H. pylori* persistent group ($P = 0.008$). In conclusion, *H. pylori* infection and old age are independent risk factors for metachronous gastric lesions after ESD in EGC.

Keywords: Gastric Cancer; Endoscopic Submucosal Dissection; Metachronous Recurrence

INTRODUCTION

Gastric cancer, which is the fourth most common cancer worldwide (1), occurs especially in Korea, Japan, China, and Far East Asia (2). *Helicobacter pylori* (*H. pylori*) infection triggers chronic gastritis (3), and causes atrophy and metaplasia (4). International Agency for Research on Cancer, the agency within World Health Organization (WHO), designates *H. pylori* as a Group 1 carcinogen (5). Results of a meta-analysis showed that *H. pylori* infection confers a two- or three-fold increase in the risk of gastric cancer development (6).

Early gastric cancer (EGC), by definition, is limited to the mucosa and submucosa layer regardless of lymph node metastasis (7). It was recommended that endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) served as a standard treatment of EGC. ESD and EMR are likely to cause complete resection and en bloc resection, even though those were technically hard to perform (7,8). It was suggested that *H. pylori* eradication could reduce the likelihood of gastric cancer occurrence (9). However, it was still controversial that *H. pylori* eradication showed preventive effects for the metachronous lesion following endoscopic resection. Japanese Gastric Cancer Association prescribed ESD for the standard treatment when absolute indication and extended indication were applied to the EGC treatment (10), and its numbers have increased. Some studies about the possibility of predicting relapse of *H. pylorus*

microorganism after treating the ESD have revealed that *H. pylori* eradication contributed to the prevention of metachronous gastric cancer (11-13). However, other scholars failed to prove its effect on prevention (14,15).

The purpose of this study was to investigate the preventive effect of *H. pylori* eradication in generating metachronous gastric neoplasm among patients who received the ESD for the EGC treatment, and find other risk factors causing metachronous gastric lesion.

MATERIALS AND METHODS

Patients and study design

Seven hundred eighty-two patients, excluding patients with a short follow-up duration under 24 months after treating with ESD, were treated with the ESD from January 2008 to December 2013 (60 months) in Gil Medical Center, Incheon, Korea. Three hundred twenty-nine patients in this group were diagnosed with the EGC. We excluded 2 patients having synchronous lesions, 12 patients missing follow-up, 35 patients implementing immediate additional gastrectomy after ESD, and 95 patients who were not tested for *H. pylori* infection using a breath test, histology, and rapid urease tests from the 329 patients stated above (Fig. 1).

Therefore, a total of 185 patients were enrolled in this retrospective study. Patients were separated into 2 groups; the nega-

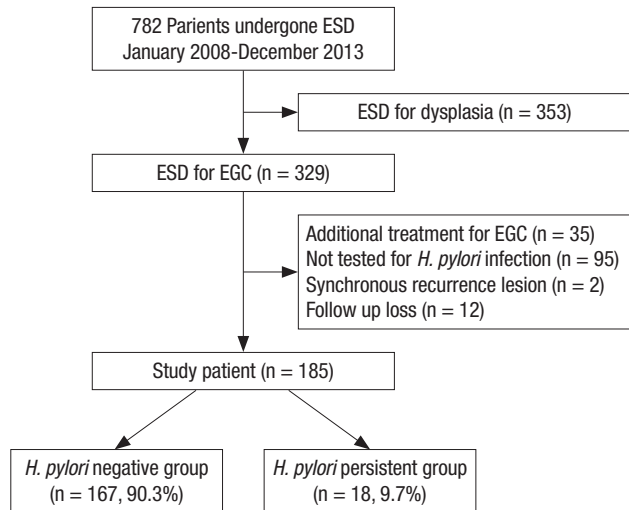


Fig. 1. Patients and study design.
ESD = endoscopic submucosal dissection, EGC = early gastric cancer.

negative group (n = 167) included patients who tested negative and experienced eradication after positive testing, while the persistent group (n = 18) encompassed patients who did not experience microorganism removal and patients who did not receive the treatment for *H. pylori* despite positive testing (Fig. 1).

Their median age was 67.4 years (45–87 years) and there were 57 smokers (30.8%) in the population. The median period of following patients was 61.5 months with a range of 24 to 96 months. Clinicopathological variables, such as age, sex, follow-up duration, number of lesions, tumor location, tumor size, endoscopic gross appearance, pathological result, depths of lesion, smoking, and drinking were captured from medical charts via clinical data retrieving and electronic medical record searching systems.

Because we reviewed patients' medical records from January 2008 to December 2013, it was not possible to receive patients' informed consents. As our study method had very low risk to patients, the IRB approved our study without requiring informed consents.

ESD technique and follow-up schedule

All ESDs were performed by using an insulated-tip knife (KD-610L; Olympus Medical, Tokyo, Japan). The typical procedure was en bloc resection that involved the procedure of marking, mucosal incision, and submucosal dissection. After treating ESD, specimens were sent to the pathology department and were labeled by the Vienna classification (16). The surveillance esophagoendoscopy was carried out after treating ESD respectively using GIF-Q240, GIF-Q260J, GIF-Q260, GIF-H260 (Olympus medical) each 3, 6, 12, 18, and 24 months. The esophagogastroduodenoscopy (EGD) was performed every year after 24 months and included a biopsy from the ESD site.

We defined recurrence as a metachronous lesion occurring over 6 months following the initial ESD. The abdominal com-

puted tomography (CT) was carried out for discerning between distant metastasis and lymph node metastasis. The CT was obtained every 6 months within the first year and every year after that.

Determination of *H. pylori* status and eradication

All the patients (n = 169) in the *H. pylori* negative group were *H. pylori* negative on the histopathology test with Hematoxylin and Eosin (HE) stain, Wright-Giemsa stain of the resected specimen, urea breath tests (UBTs), and rapid urease tests (HP kit; CKD Bio Corp., Seoul, Korea). However, the *H. pylori* positive group was defined when *H. pylori* showed a positive on at least 1 test among all of the tests. The treatment of *H. pylori* eradication therapy was carried out based on Korean guidelines for *H. pylori* infection (17). The first line treatment included amoxicillin, clarithromycin and the standard dose of proton-pump inhibitor (PPI), taken twice a day for a week. If it failed, the second line regimen was administered for a week. This regimen consisted of 4 drugs: metronidazole 250 mg 3 times a day, tetracycline 500 mg 4 times a day, bismuth 240 mg 4 times a day and PPI standard dose twice a day. The UBT and rapid urease tests were used to confirm the successful *H. pylori* eradication. The negative group was defined when 2 tests were negative.

Histopathological examination of gastric lesion

Our 2 expert pathologists examined both resected specimens through the ESD and specimens through the biopsy. Historical classification of the gastric cancer complied with the new Japanese classification (16). The occurrence of metachronous neoplasm was defined when the dysplasia and carcinoma occurred more than 6 months after ESD.

Statistical analysis

Baseline data were obtained from our prospectively collected electronic medical records. All numerical variables, such as age, follow-up duration, and maximum diameters of lesions, were expressed as the mean standard deviation. Chi-square test and Fisher's exact test were applied to compare 2 groups and metachronous recurrence. Student's t-test was used for non-categorical variables in the intergroup comparison of clinical pathological characteristics. The threshold for statistical significance was set at $P < 0.05$. Recurrence-free survival and the incidence of metachronous gastric cancer were calculated using the Kaplan-Meier method, and compared between 2 groups by log-rank test. A Cox proportional hazards model and multivariate analyses were used for risk assessment. Statistical analyses were performed using the Statistical Package for Social Science Version 18.0 (SPSS Inc., Chicago, IL, USA).

Ethics statement

The study protocol was approved by the Institutional Review

Table 1. Clinicopathologic characteristics of patients with and without metachronous lesion

Parameters	Patients with ML (n = 24)	Patients without ML (n = 161)	P value
Mean age, yr	71.25 ± 8.06	66.82 ± 10.09	
< 70	9 (37.5)	95 (59.0)	0.048
≥ 70	15 (62.5)	66 (41.0)	
Sex (male)	19 (79.2)	122 (75.8)	0.716
Location			0.374
Upper 1/3	0 (0.0)	10 (6.2)	
Middle 1/3	9 (37.5)	43 (26.7)	
Lower 1/3	15 (62.5)	108 (67.1)	
Gross appearance			0.731
Elevated	2 (8.3)	18 (11.2)	
Flat	7 (29.2)	59 (36.6)	
Depressed	15 (62.5)	84 (52.2)	
Maximum diameter of lesion, mm	14.08 ± 7.96	14.74 ± 8.61	0.248
Multiplicity	1 (4.2)	5 (3.1)	0.571
Depth of invasion			0.476
M	23 (95.8)	143 (88.8)	
SM	1 (4.2)	18 (11.2)	
H.P. status			0.003
Eradicated	17 (70.8)	150 (93.2)	
Persistent	7 (29.2)	11 (6.8)	
Smoking	4 (16.7)	53 (32.9)	0.108
Alcohol	11 (45.8)	73 (45.3)	0.964

Values are presented as mean ± SD or number (%). ML = metachronous lesion, M = mucosa, SM = submucosa, H.P. = *Helicobacter pylori*.

Board of Gachon University Gil Medical Center (GAIRB No. 2016-173). The IRB approved our study without informed consents.

RESULTS

A total of 185 patients were enrolled in our study. Of the 185 patients enrolled, 141 were male and 44 were female with a median age of 67.4. During the follow-up period, metachronous lesions were found in 24 (13.0%) of the 185 patients. The clinicopathological characteristics of patients according to the development of metachronous neoplasms are shown in Table 1. There were no statistically significant differences between the 2 groups in terms of the sex ratio, smoking and alcohol consumption history, location and gross appearance, the diameter, multiplicity or the depth of the tumor. However, there were statistically significant differences in age ($P = 0.048$) and *H. pylori* status ($P = 0.003$) between the patients with metachronous lesions and without metachronous lesions.

Metachronous lesions consisted of adenocarcinoma (12 patients, 50.0%), high grade dysplasia (7 patients, 29.1%), and low grade dysplasia (5 patients, 20.9%). *H. pylori* persistent group included 16 patients who did not receive eradication treatment though the test result showed positive, and 2 patients consistently appearing positive results of *H. pylori* examinations after second line therapy. The median time to recurrence was 24 months, with a range of 6 to 75 months. We calculated cumulative incidence of the metachronous recurrence between the *H. py-*

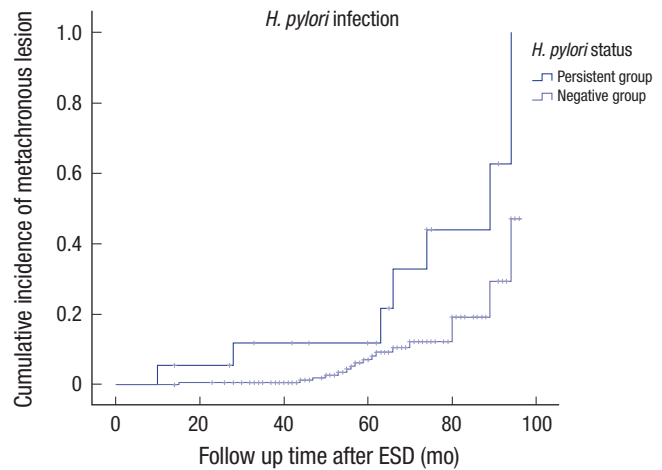


Fig. 2. Cumulative incidence of the metachronous recurrence (*H. pylori*). ESD = endoscopic submucosal dissection.

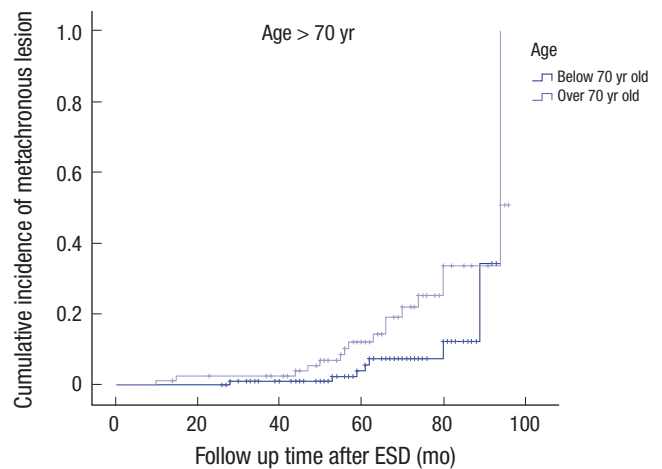


Fig. 3. Cumulative incidence of the metachronous recurrence (age). ESD = endoscopic submucosal dissection.

lori persistent group and negative group using Kaplan-Meier method. The risk of cumulative incidence of the metachronous recurrence in the *H. pylori* persistent group was higher than the negative group ($P = 0.008$) (Fig. 2). We also analyzed a risk of cumulative incidence of the metachronous recurrence in age by using Kaplan-Meier method. There was higher risk in the over 70-year-old group ($P = 0.025$) (Fig. 3).

DISCUSSION

Our study shows that *H. pylori* could play an important role in developing metachronous cancer after ESD for EGC. Metachronous lesions occurred in 7 cases in the persistent group (38.8%) and 17 cases in the negative group (10.2%) during 61.1 months (median) (Table 1). There was little clinicopathological difference in the metachronous lesion group. However, there was substantial difference in both the *H. pylori* persistent group and

the over 70-year-old group. These results suggest that the existence of *H. pylori* and old age increase the likelihood of metachronous lesion. Our study was based on previous studies that reported *H. pylori* infection plays an important role in the development of gastric cancer.

In Korea, endoscopic resection, including ESD, is the mainstream modality for EGC without metastasis (18). Recently, several studies reported that ESD for EGC treatment achieved good long-term outcomes and acceptable complication rates (7,19-22). In metachronous recurrence, 1 large population retrospective study reported the 5-year, 7-year, and 10-year cumulative incidence of metachronous gastric cancer were 9.5%, 13.1%, and 22.7%, retrospectively (23). This was distinguished from the cumulative incidence (6.1%) who underwent surgery (24). This discrepancy can be explained by the existence of tiny invisible lesions at the moment of ESD, the ability of ESD to offer an organ-sparing approach, a contribution to the better quality of life, and atrophic mucosa that can be a risk factor for cancer. It was reported that there was no difference in overall survival of patients who received the EMR on EGC, unlike the generation of metachronous lesion (25,26).

Gastric carcinogenesis is a complex and multifactorial process with many risk factors including non-ulcer dysplasia, active gastric ulcers, degree of mucosal atrophy, and *H. pylori* infection (27,28). The effect of *H. pylori* eradication on gastric mucosa is that neutrophilic infiltration disappears and infiltration with lymphocytes and plasma cells will be significantly reduced in the gastric mucosa. Then this retards the process of the precancerous lesion (29). The randomized trial reported that *H. pylori* eradication has a preventative effect to put the blocks on intestinal metaplasia and gastric atrophy (30). This can reduce the metachronous lesion occurrence from ESD patients after *H. pylori* eradication. However, moderate to severe atrophy or intestinal metaplasia may represent a 'point of no return' (31,32). Therefore, the prompt eradication of *H. pylori* reduces the process of atrophy, and this is helpful to prevent gastric cancer (33). The removal of *H. pylori* microorganism after ESD is necessary for the prevention of gastric metachronous. According to our study, *H. pylori* eradication decreased metachronous lesions, which is one of the topics in recent meta-analysis studies (34). The increase of metachronous lesions in patients over 70 years old was a meaningful result from our data. A study found that old age was an independent risk factor of metachronous lesion, and *H. pylori* eradication on EGC after endoscopic resection did not increase metachronous lesions (14). In the other 10-year follow-up Japanese study, preventing gastric cancer by *H. pylori* eradication showed 100% effectiveness in patients under 40 years of age, and only 45% effectiveness in patients over 70 years of age (35). The occurrence of metachronous lesion in old age can be explained by the 'point of no return' idea (31). The *H. pylori* eradication from elderly patients, who proceeded

to intestinal metaplasia and severe atrophy with a long-term *H. pylori* infection, could not prevent EGC. Other environmental factors, such as food, tobacco, and socioeconomic status based on age, are possible to generate metachronous lesions in elderly patients (36). Therefore, regular inspection is necessary for elderly patients, even if *H. pylori* is eradicated.

We think a prospective cohort study is needed for the exact multivariate analysis of both old age and *H. pylori* infection. Several limitations of this study require discussion. First, this was only a single center, retrospective study. This could induce selection bias for the generalization of the results. Second, the persistent *H. pylori* infection group was a small population. We had tried to determine *H. pylori* status through medical records, but had to enroll a small number of patients compared to the number of patients in the *H. pylori* negative group. This was due to the absence of examining a large number of patients with a *H. pylori* test. Finally, we did not analyze the background atrophy status and intestinal metaplasia, which might affect the metachronous recurrence and could be a confusing factor. Despite its limitations, this study is different from previous studies. First, we were covering only ESD from EGC. Second, we included metachronous lesions in all dysplasia as well as in malignancy.

In conclusion, the risk of metachronous recurrence after ESD for EGC was higher in the *H. pylori* persistent group than the negative group. Old age is an independent risk factor for patients after ESD for EGC. Therefore, a lot of clinicians should consider *H. pylori* eradication and regular surveillance, especially in patients with old age, after ESD for EGC.

DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceptualization: Chung JW. Data curation: Jeong SH, Kwon KA, Kim YJ, Kim KO, Park DK. Formal analysis: Chung CS. Investigation: Chung CS. Writing - original draft: Chung CS, Woo HS. Writing - review & editing: Chung CS, Woo HS.

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