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Original Article

Early versus Late Eradication of *Helicobacter pylori* after Endoscopic Submucosal Dissection of Gastric Neoplasms: A Prospective, Multicenter, Randomized, Controlled Study

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Background/Aims: *Helicobacter pylori* is a well-known gastric carcinogen, and its eradication is an important therapeutic strategy to prevent the development of metachronous lesions following endoscopic submucosal dissection (ESD). However, the optimal timing for *H. pylori* eradication following ESD remains unclear.

Methods: In this multicenter, prospective, randomized trial, 191 patients undergoing ESD for gastric neoplasms were randomly assigned to either an early (3 to 5 days) or late (8 to 9 weeks) eradication group after ESD. The primary outcome was the rate of successful *H. pylori* eradication. Secondary outcomes included the tolerability and side effects of eradication therapy in both groups.

Results: A total of 149 patients were included in the per-protocol analysis (75 in the early eradication group and 74 in the late eradication group) after excluding patients who required surgery or were lost to follow-up. The early eradication group showed a significantly higher eradication rate compared to the late eradication group (early 80.0%, late 64.9%; p=0.045). However, the tolerability and side effects of the eradication therapy did not differ between the groups. In multivariate analysis, early initiation of eradication therapy after ESD was an independent predictor of successful eradication (odds ratio, 2.30; 95% confidence interval, 1.04 to 5.05; p=0.038).

Conclusions: Early attempts to eradicate *H. pylori* following ESD significantly increased eradication success rates without increasing the incidence of side effects. Therefore, early attempts to eradicate *H. pylori* after ESD may be the best option for successful eradication. (ClinicalTrials.gov identifier NCT02921399) **(Gut Liver, 2025;19:821-828)**

Key Words: *Helicobacter pylori*; Endoscopic submucosal dissection; Gastric neoplasms

INTRODUCTION

Helicobacter pylori is a significant gastric pathogen responsible for gastroduodenitis, peptic ulcer disease, and gastric malignancies, including mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma.[1-4] Endoscopic submucosal dissection (ESD) stands as a widely accepted treatment for gastric dysplasia and select cases of early gastric cancer, offering advantages such as stomach preservation, improved quality of life, and reduced healthcare costs. However, the risk of metachronous gastric neoplasms in the remnant stomach post-ESD surpasses that after gastrectomy.[5] Hence, *H. pylori* eradication proves essential in preventing metachronous lesions following ESD.[6,7]

Traditionally, triple therapy comprising proton pump inhibitor (PPI), amoxicillin, and clarithromycin has been the primary regimen for *H. pylori* eradication.[8] However, clarithromycin resistance has escalated, emerging as a critical factor in treatment failure. In recent years, first-line therapy eradication rates in South Korea have decreased to in range of 74.6% to 75.8%.[9-11] Although culture-based an-

timicrobial susceptibility testing is advocated to overcome antibiotic resistance, its routine implementation in clinical practice remains limited. Hence, it becomes imperative to identify easily applicable factors that bolster eradication rates in clinical settings. Previous studies have indicated that the active reparative phase of gastric ulcers serves as an independent prognostic factor for successful eradication.[12] These findings suggest that initiating eradication treatment during the active stage of ESD-induced iatrogenic ulcers may significantly enhance eradication success rates. In line with this, our previous retrospective study unveiled that administering eradication treatment within 2 weeks post-ESD during the active reparative phase of ESD-induced ulcers yielded a markedly higher success rate compared to treatment post-8 weeks during the scarring phase of ESD-induced ulcers.[13] However, this study was limited by its retrospective design within a single institution.[12,13] Therefore, we conducted a multicenter, randomized, prospective study to ascertain whether the optimal timing of eradication post-ESD could influence the eradication success rate.

MATERIALS AND METHODS

1. Study design and patients

This prospective multicenter randomized controlled study involved inpatients who underwent ESD for gastric neoplasia between January 2017 and June 2021 at three referral hospitals: Gangnam Severance Hospital, Yongin Severance Hospital, and Incheon St. Mary's Hospital. Patients aged 19 to 75 years who underwent ESD and tested positive for *H. pylori* infection via the rapid urease test were included. Exclusion criteria comprised individuals with a history of gastric surgery or endoscopic resection, prior *H. pylori* eradication therapy, recent use (within the preceding 2 weeks) of drugs impacting *H. pylori* infection test results (such as PPIs, histamine-2 receptor blockers, or antibiotics), known hypersensitivity to antibiotics and PPIs, or at the discretion of the investigator.

All patients provided written informed consent prior to participating in the study. Patients were randomly assigned to either the early eradication group (3 to 5 days after ESD) or the late eradication group (8 weeks±5 days after ESD) based on computer-generated random numbers. Participants were assigned to treatment groups using a simple randomization process performed by a computer-generated program developed by an independent investigator. The randomization numbers were sealed in opaque envelopes by a research assistant not involved in data collection and remained under lock until the last patient was included. The study protocol was approved by the institutional review boards of each institution before initiation (approval numbers: Gangnam Severance Hospital, 3-2016-0175; Yongin Severance Hospital, 9-2020-0053; Incheon St Mary's Hospital, OC17OEDE0090). This trial was registered in the International Clinical Trials Registry Platform (No. NCT02921399).

2. ESD procedure

All ESD procedures were performed on hospitalized patients under intravenous sedation. A video endoscope (GIF-HQ290, GIF-Q260, GIF-H260; Olympus, Tokyo, Japan) was used for procedure. Lesion margins were marked with argon plasma coagulation (VIO 300D; ERBE, Tübingen, Germany), followed by submucosal injection of epinephrine (0.01 mg/mL) and indigo carmine. A Dual knife (KD-650Q; Olympus) or Insulated-tip knife (KD-610L; Olympus Optical, Tokyo, Japan) was used for incision and dissection, with hemostasis achieved using hemoclips or hemostatic forceps. Following ESD, chest and abdominal radiographs were routinely obtained immediately post-procedure and on the following day to monitor for complications, including perforation or pneumonia.

3. Protocol

Following ESD, we conducted a rapid urease test (Asan *Helicobacter* test; Asan Pharmaceutical Co., Ltd., Seoul, Korea) to detect *H. pylori* infection. Infection was confirmed by a positive rapid urease test result. Subsequently, patients were randomly allocated to either the early (3 to 5 days after ESD) or late (8 weeks±5 days after ESD) eradication groups. All patients underwent ESD and received intravenous pantoprazole twice daily on the day of ESD and the following day. In the early eradication group, patients were administered a 7-day PPI-based triple therapy (i.e., pantoprazole, amoxicillin 1.0 g, clarithromycin 500 mg; all taken twice daily), followed by oral administration of pantoprazole 40 mg for 7 weeks. In the late eradication group, patients received oral pantoprazole (40 mg) for 7 weeks, followed by 7 days of PPI-based triple therapy. All patients underwent endoscopy 12 weeks±5 days after ESD to assess the condition of ESD-induced ulcers. The success of *H. pylori* eradication was determined using a urea breath test conducted 13 weeks±5 days after ESD (Fig. 1). Patients who were lost to follow-up before confirmation of eradication were excluded from the final analysis.

4. Data collection

We prospectively collected clinicopathological factors including age, sex, smoking status, alcohol consumption, pre-existing comorbidities (e.g., hypertension, diabetes mellitus, chronic kidney disease, cardiovascular disease,

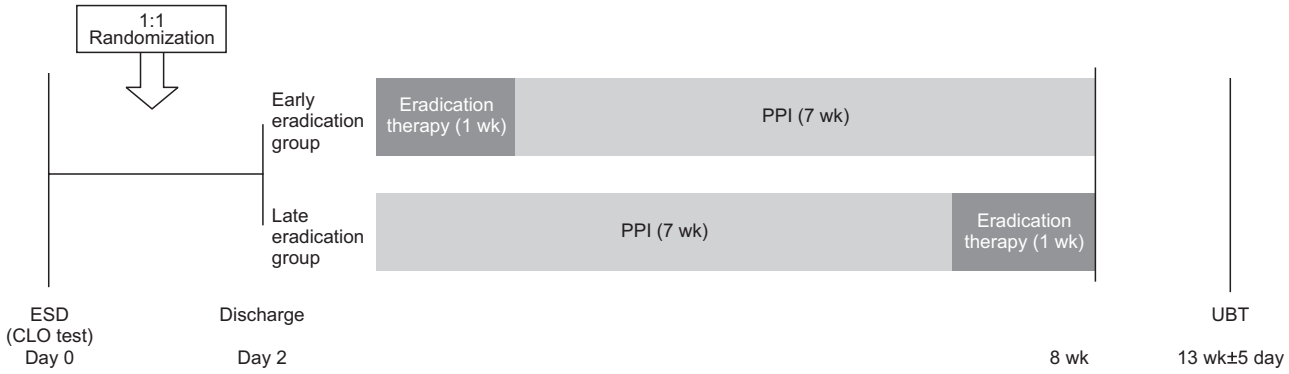

Fig. 1. Study protocol. ESD, endoscopic submucosal dissection; PPI, proton pump inhibitor; UBT, urea breath test.

and others), size and location of ESD-induced ulcers, endoscopic findings of background mucosa (e.g., mucosal atrophy or intestinal metaplasia), histopathological results, tolerability, and side effects of eradication therapy. Atrophic gastric mucosa was defined as a whitish-to-yellowish color change, visible submucosal vessels, and a decrease in rugal folds. Intestinal metaplasia was characterized by a metaplastic mucosa with fine or coarse plaques. The sizes of the ESD-induced ulcers were extrapolated from the excised specimens.

5. Outcome

The primary outcome was the success rate of *H. pylori* eradication in the early- and late-eradication groups. The secondary outcomes included treatment tolerability and the frequency of self-reported side effects.

Patients were requested to return upon completion of therapy for physical evaluation and to assess the tolerability and side effects of the eradication therapy. One investigator at each center evaluated treatment tolerability and self-reported side effects during the interview. Initially, we posed open-ended questions about side effects, followed by specific inquiries regarding anticipated side effects. The questionnaire evaluated gastrointestinal side effects including taste disturbances, decreased appetite, nausea, vomiting, epigastric pain, bloating, diarrhea, constipation, and skin rash, focusing specifically on symptom onset, severity, and frequency. Symptom severity was categorized using a 4-point scale: 0 (none), 1 (mild), 2 (moderate), and 3 (severe). Treatment tolerability was evaluated using a 5-point scale as follows: 1, no side effects observed; 2, mild side effects without interference in daily activities; 3, moderate side effects causing minimal interference with daily activities; 4, severe side effects significantly affecting daily activities but not requiring treatment discontinuation; and 5, severe side effects necessitating discontinuation of treatment.

6. Sample size calculations

A previous retrospective study indicated that the rates of *H. pylori* eradication success in the early and late groups were 90.0% and 72.4%, respectively[13]. With an α value of 0.05 and a power of 80%, the estimated sample size required was 148 patients. Considering a dropout rate of 10%, a total of 166 patients were deemed necessary.

7. Statistical analysis

Primary and secondary outcomes were analyzed using a per-protocol set. Between-group comparisons of clinical characteristics were performed using the chi-square test or the Fisher exact test for categorical variables and the Student t-test for continuous variables. Factors influencing *H. pylori* eradication rates underwent logistic regression analysis. Statistical significance was defined as $p<0.05$. All statistical analyses were conducted using SPSS (version 25.0; SPSS Inc., Chicago, IL, USA).

RESULTS

1. Patient characteristics

Of the 402 screened patients, 191 were included in the randomization protocol, with 97 allocated to the early eradication group and 94 to the late eradication group. Following randomization, 22 patients in the early eradication group and 20 in the late eradication group dropped out due to additional operations necessitated by non-curative resection, poor compliance (taking less than 80% of the total medication), loss to follow-up, or personal reasons. Ultimately, 75 patients in the early eradication group and 74 in the late eradication group were included in the per-protocol set analysis (Fig. 2). The overall success rate of *H. pylori* eradication in this study was 72.5% (108/149). The clinicopathological characteristics of the study population, stratified by early eradication (n=75) and late eradication

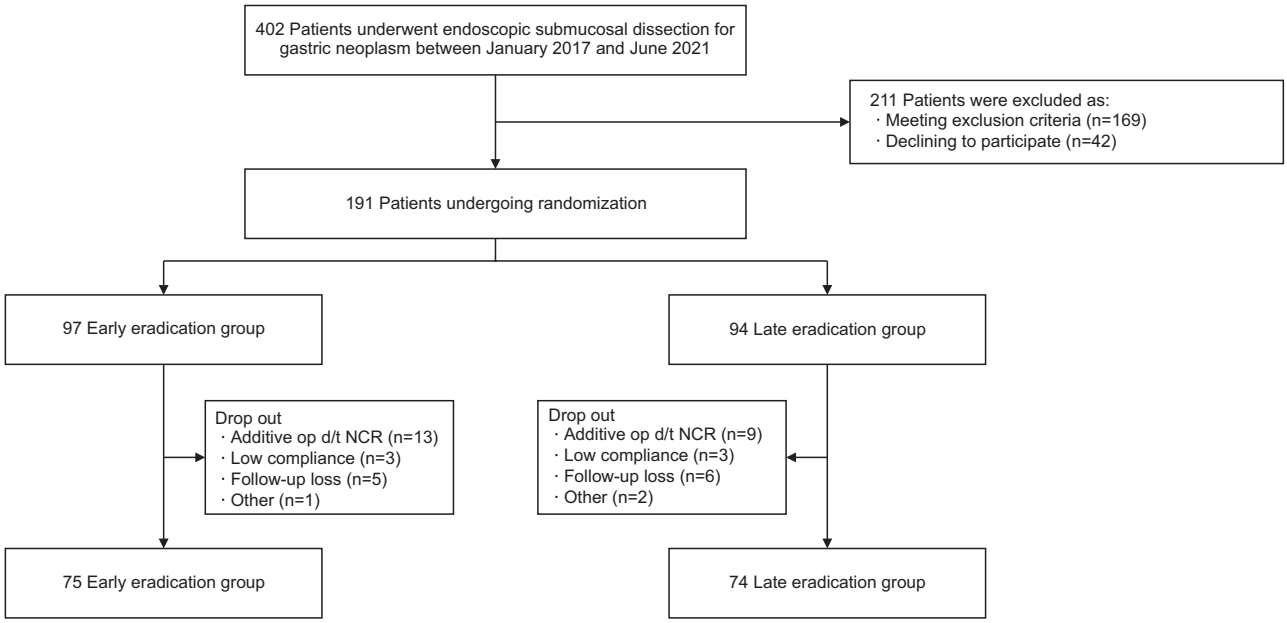

Fig. 2. Study flow diagram. Additive op d/t NCR, additive operation due to non-curative resection.

(n=74), are presented in Table 1. Age, sex, smoking, alcohol consumption, underlying disease, mean size and location of ESD-induced ulcers, background mucosal status, and tumor histology did not differ significantly between the groups (Table 1).

2. Univariate analysis affecting the *H. pylori* eradication rate

Baseline characteristics associated with the success of *H. pylori* eradication therapy are summarized in Table 2. Early attempts at eradication therapy demonstrated a higher eradication rate compared to late attempts. The eradication success group had smaller ESD-induced ulcers than those in the eradication failure group. Age, sex, smoking, alcohol consumption, underlying disease, location of ESD-induced ulcers, background mucosal status, tumor histology, treatment tolerability, and side effects of eradication therapy did not show significant differences between the groups.

3. Primary outcome

The early eradication group (n=75) achieved a significantly higher eradication rate than the late eradication group (n=74) (early 80.0%, late 64.9%; p=0.045) (Fig. 3). Early initiation of *H. pylori* eradication and ESD-induced ulcer size were identified as significant independent predictors of eradication success in multivariate analysis (odds ratio, 2.30; 95% confidence interval, 1.04 to 5.05; p=0.038) (Table 3).

4. Secondary outcomes

There were no significant differences between the early and late eradication groups in terms of treatment tolerability, and none of the patients experienced severe adverse effects. In addition, there was no 30-day post-ESD bleeding in either the early or late eradication groups. The most frequently reported side effect was taste distortion, followed by loss of appetite, nausea or vomiting, diarrhea, and epigastric discomfort (Table 4).

DISCUSSION

This study represents the first multicenter randomized controlled trial aimed at investigating the eradication rate of *H. pylori* based on the timing of eradication therapy following ESD in patients diagnosed with early gastric cancer or dysplasia. The findings indicated a significantly higher *H. pylori* eradication rate in the early eradication group (within 3 to 5 days after ESD) compared to the late eradication group (8 to 9 weeks post-ESD) (early 80.0%, late 64.9%: odds ratio, 2.30; p=0.038). There were no discernible differences in the tolerability or side effects of the eradication therapy between the early and late eradication groups.

Previous studies have reported higher success rates of *H. pylori* eradication in patients with peptic ulcer disease compared to those with non-ulcerative dyspepsia.[14-16] Additionally, the presence of an active-stage gastric ulcer has been identified as a positive predictor for successful eradication.[12] Building upon these findings, we conducted a retrospective study to explore the successful eradication rate according to the timing of eradication, categorized

Table 1. Clinical Characteristics of the Early Eradication Group and the Late Eradication Group

Variable	Early eradication group (n=75)	Late eradication group (n=74)	p-value
Age, mean±SD, yr	64.3±9.8	63.1±9.5	0.452
Sex			0.376
Male	55 (73.3)	49 (66.2)	
Female	20 (26.7)	25 (33.8)	
Smoking			0.129
Current	15 (20.0)	6 (8.1)	
Ex-smoking	14 (18.7)	16 (21.6)	
Never	46 (61.3)	52 (70.3)	
Drinking			0.869
Yes	32 (42.7)	33 (44.6)	
No	43 (57.3)	41 (55.4)	
Pre-existing comorbidity			0.124
No	39 (52.0)	38 (51.4)	
Hypertension	20 (26.7)	26 (35.1)	
Diabetes mellitus	10 (13.3)	9 (12.2)	
Chronic kidney disease	1 (1.3)	0	
Cardiovascular disease	5 (6.7)	0	
Others	0	1 (0.7)	
ESD-induced ulcer size, mean±SD, mm	30.3±15.1	29.8±13.5	0.837
ESD-induced ulcer location			0.905
Upper	8 (10.7)	7 (9.5)	
Middle	16 (21.3)	18 (24.3)	
Lower	51 (68.0)	49 (66.2)	
Endoscopic atrophy			0.992
Yes	74 (98.7)	73 (98.6)	
No	1 (1.3)	1 (1.4)	
Endoscopic IM			0.856
Yes	53 (70.7)	54 (93.0)	
No	22 (29.3)	20 (27.0)	
Tumor histology			0.255
Low grade dysplasia	18 (24.0)	26 (35.1)	
High grade dysplasia	8 (10.7)	9 (12.2)	
Cancer	48 (64.0)	39 (52.7)	
Hyperplasia	1 (1.3)	0	

Data are presented as number (%) unless otherwise indicated.
ESD, endoscopic submucosal dissection; IM, intestinal metaplasia.

into active and scarring stages of ESD-induced ulcers. This analysis revealed that initiating eradication treatment within 2 weeks after endoscopic resection, during the active reparative phase of ESD-induced ulcers, resulted in a success rate of 90%. Conversely, treatment initiated after 8 weeks during the scarring phase of ESD-induced ulcers yielded a success rate of 72.4%, indicating a significant difference between the two groups.[13] However, this prior study had a retrospective design, encompassing both endoscopic mucosal resection and ESD, variations in the duration of eradication treatment, and lacked a clear definition of early or late eradication treatment.

In this prospective study, the early eradication group achieved a significantly higher eradication rate than the late eradication group, consistent with previous retrospective studies.[12,13] The underlying mechanism for this difference remains unclear, yet several possible explanations exist. First, inflammatory responses during active ulcer repair likely influence eradication outcomes. Previous studies have noted that a higher eradication rate correlates with intense neutrophilic infiltration of the gastric antrum.[17-19] During the active repair phase, the loss of gastric mucus and epithelial barriers may facilitate the penetration of charged antibiotics from the stomach lumen, enhancing systemic drug delivery through altered epithelial and vascular permeability. This altered permeability, combined with enhanced inflammatory responses, could render *H. pylori* more vulnerable to antibiotic agents, thus potentially increasing the eradication success rate during this period. Second, intragastric pH may have contributed to the disparity in eradication rates between the two groups. The early eradication group, receiving a double dose of intravenous PPIs for 2 days after ESD, might have maintained a higher intragastric pH compared to the late eradication

Table 2. Univariate Analysis of Factors Affecting the *Helicobacter pylori* Eradication Rate

Variable	Eradication success (n=108)	Eradication failure (n=41)	p-value
Age, mean±SD, yr	62.9±9.3	65.8±10.4	0.307
Sex			0.518
Male	77 (71.3)	27 (65.9)	
Female	31 (28.7)	14 (34.1)	
Smoking			0.230
Current	18 (16.7)	3 (7.3)	
Ex-smoking	23 (21.3)	7 (17.1)	
Never	67 (62.0)	31 (75.6)	
Drinking			0.151
Yes	51 (47.2)	14 (34.1)	
No	57 (52.8)	27 (65.9)	
Pre-existing comorbidity			0.101
No	61 (56.5)	16 (39.0)	
Hypertension	30 (27.8)	16 (39.0)	
Diabetes mellitus	13 (12.0)	6 (14.7)	
Chronic kidney disease	1 (0.9)	0	
Cardiovascular disease	3 (2.8)	2 (4.9)	
Others	0	1 (2.4)	
ESD-induced ulcer size, mean±SD, mm	28.6±14.5	33.7±13.2	0.043
ESD-induced ulcer location			0.658
Upper	12 (11.1)	3 (7.3)	
Middle	23 (21.3)	11 (26.8)	
Lower	73 (67.6)	27 (65.9)	
Endoscopic atrophy			0.474
Yes	107 (99.1)	40 (97.6)	
No	1 (0.9)	1 (2.4)	
Endoscopic IM			0.857
Yes	78 (72.2)	29 (70.7)	
No	30 (27.8)	12 (29.3)	
Tumor histology			0.378
Low grade dysplasia	30 (27.8)	14 (34.1)	
High grade dysplasia	15 (13.9)	2 (4.9)	
Cancer	62 (57.4)	25 (61.0)	
Hyperplasia	1 (0.9)	0	
Timing of *H. pylori* eradication			0.045
Early (3–5 day after ESD)	60 (55.5)	15 (36.6)	
Late (8 wk±5 day after ESD)	48 (44.5)	26 (63.4)	

Data are presented as number (%) unless otherwise indicated.
ESD, endoscopic submucosal dissection; IM, intestinal metaplasia.

Table 3. Multivariate Analysis of Factors Affecting the *Helicobacter pylori* Eradication Rate

Factor	Odds ratio (95% CI)	p-value
Sex		
Female	1	
Male	0.81 (0.33– 2.02)	0.653
Age	0.96 (0.92–1.01)	
ESD-induced ulcer size	0.96 (0.93–0.99)	0.011
Smoking		
Current	3.38 (0.76–15.00)	0.109
Ex-smoking	1.71 (0.58–5.03)	0.332
Never	1	
Timing of *H. pylori* eradication		
Early (3–5 day)	2.30 (1.04–5.05)	0.038
Late (8–9 wk)	1	

CI, confidence interval; ESD, endoscopic submucosal dissection.

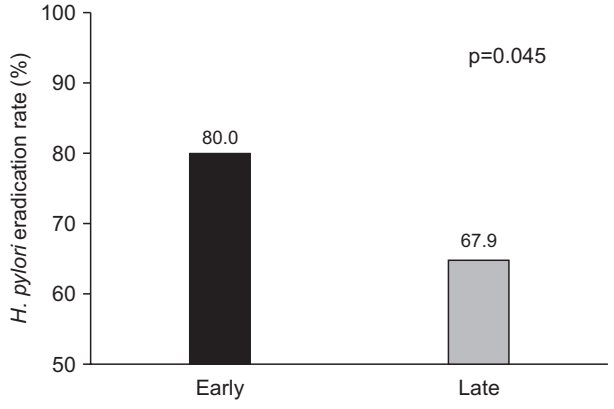

Fig. 3. *Helicobacter pylori* eradication rate according to the timing of eradication therapy after endoscopic submucosal dissection.

Table 4. Side Effects According to the Timing of *Helicobacter pylori* Eradication

Variable	Early eradication group (n=75)	Late eradication group (n=74)	p-value
Treatment tolerability			0.330
No side effect	56 (74.7)	50 (67.6)	
Mild side effect	19 (25.3)	22 (29.7)	
Moderate side effect	0	2 (2.7)	
Severe side effect	0	0	
Side effects			0.676
No	56 (74.7)	50 (67.6)	
Yes	19 (25.3)	24 (32.4)	
Taste distortion	9 (12.0)	15 (20.3)	
Loss of appetite	5 (6.7)	3 (4.1)	
Nausea or vomiting	2 (2.7)	4 (5.4)	
Epigastric pain	2 (2.7)	1 (1.4)	
Diarrhea	3 (4.0)	2 (2.7)	
Post-ESD bleeding	0	0	NA

ESD, endoscopic submucosal dissection; NA, not available.

group. Higher intragastric pH levels are associated with a greater success rate of *H. pylori* eradication treatment,[20] possibly elucidating the higher eradication success rate in the early eradication group. Finally, another potential contributing factor to the difference in eradication rates could be the recommended dietary modifications following ESD. Patients were advised to consume a soft diet for the initial 5 to 7 days post-ESD. This dietary recommendation could potentially influence the eradication rate by affecting the gastric emptying rate of the soft diet.[21]

The successful eradication of *H. pylori* is crucial in preventing the development of metachronous gastric cancer or dysplasia following endoscopic resection of gastric neoplasms.[22] Numerous studies have demonstrated that successful eradication of *H. pylori* reduces the risk of recurrence of metachronous gastric cancer or dysplasia compared to non-eradicated groups.[22-24] However, few studies have investigated the optimal timing of eradication treatment after endoscopic resection for gastric neoplasms. The results of the present study revealed that initiating eradication treatment immediately after ESD significantly improved the success rate of eradication treatment. Additionally, there were no differences in tolerability or side effects of eradication therapy between the early and late eradication treatment groups. Therefore, early initiation of *H. pylori* eradication after ESD is considered the optimal time to increase the eradication rate without drug-related side effects.

This study has several limitations that must be considered. First, antibiotic susceptibility testing was not performed to evaluate the primary bacterial resistance to clarithromycin, which is a major factor affecting *H. pylori* eradication success. Second, the eradication treatment regimen consisted of a 7-day PPI-based triple therapy. At the initiation of the study, the domestic guidelines for *H. pylori* treatment recommended this regimen as the first-line treatment. Moreover, the use of only these antibiotics is permitted as a first-line treatment within the Korean medical insurance system, limiting our options. Finally, our results are restricted to South Korea and must be generalized to other ethnicities or countries with caution. In the future, a prospective, multicenter, multinational, randomized controlled study with a larger sample size, including antibiotic susceptibility testing, would provide more robust evidence.

In conclusion, initiating *H. pylori* eradication therapy within ≤5 days after ESD of gastric neoplasm significantly improves eradication success rates without increasing drug side effects. Thus, early initiation of *H. pylori* eradication following ESD may represent the optimal approach for achieving successful eradication.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Study conception and design: C.W.H., D.H.J., J.H.K., H.P., Y.H.Y. Data analysis and interpretation: C.W.H., D.H.J., J.H.K., H.P., Y.H.Y. Drafting of the manuscript:

C.W.H., D.H.J., Y.H.Y. Critical revision of the manuscript for important intellectual content: Y.H.Y. Approval of final manuscript: all authors.

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