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ORIGINAL ARTICLE

Helicobacter pylori prevalence and its spontaneous eradication rate after distal or proximal gastrectomy for gastric cancer: A multicenter prospective cohort study

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Abstract

Background: *Helicobacter pylori* (*H. pylori*) eradication is recommended in patients undergoing endoscopic resection for early gastric cancer to reduce recurrence. However, due to the possibility of spontaneous regression secondary to dynamic changes in the remnant stomach, the immediate eradication after gastrectomy for *H. pylori* carriers remains unclear. This study aimed to investigate the prevalence of *H. pylori* in Japanese patients with gastric cancer and the spontaneous eradication rate after distal or proximal gastrectomy.

Methods: This multicenter prospective cohort study was conducted at 22 institutions. Eligibility criteria was patients over 20 years planned to undergo R0 gastrectomy for gastric cancer. The primary endpoint was spontaneous eradication rate 1 year after distal or proximal gastrectomy. The prevalence of *H. pylori* infection before surgery and clinical features related to spontaneous eradication were examined.

Results: A total of 1247 patients were included in this study. The preoperative *H. pylori* status was positive in 756 patients and negative in 491. Seventy-nine of the negative patients had an eradication history, totaling 835 (67%) patients preoperatively infected with *H. pylori*. The infection status of 541 patients was examined 1 year postoperatively; 285 were negative, with a 52.7% spontaneous eradication rate. Spontaneous eradication was significantly higher in male and older patients (>70 years); other factors, such as histological type, gastrectomy method and adjuvant chemotherapy presence, did not affect the rate.

Conclusions: As spontaneous *H. pylori* eradication occurred in more than half of the analyzed patients, retesting for *H. pylori*. should be considered before postoperative eradication therapy (UMIN000020280).

KEYWORDS
gastrectomy, gastric cancer, *H. pylori*, spontaneous eradication

1 | INTRODUCTION

Gastric cancer (GC) is the fifth most common and third most deadly cancer, with more than 780 000 annual deaths worldwide.[1–3] *Helicobacter pylori* (*H. pylori*) is known to play an important role in GC initiation,[4,5] and the eradication of *H. pylori* was reported to confer a long-term protection against gastric cancer even in high-risk populations, especially for infected individuals without precancerous gastric lesions at baseline.[6] Based on these studies, an unequivocal role for *H. pylori* in the development of gastric cancer was established and the eradication of *H. pylori* may be an effective means of gastric cancer prevention.

H. pylori eradication is widely accepted to reduce recurrence and improve survival in patients undergoing endoscopic resection for early gastric cancer (EGC),[7–9] and most guidelines recommend such eradication after endoscopic treatment for EGC. In the presence of premalignant lesions of GC, such as atrophic gastritis and intestinal epithelialization, *H. pylori* infection increases the risk of GC by 4–6 times compared to patients without infection.[10–13]

Nakane et al. reported that the 5-year cumulative remnant GC incidence rate after gastrectomy was 2.9%.[14] However, the relationship between remnant GC and *H. pylori* infection remains unclear. A large cohort study demonstrated that *H. pylori* eradication using medication after subtotal gastrectomy resulted in significant benefits in overall and gastric cancer-specific survival rates.[15,16] However, only few studies have reported the spontaneous regression of *H. pylori* after subtotal gastrectomy for peptic ulcers or GC.[17,18] Postoperative changes in *H. pylori* infection status are suggested to be associated with dramatic changes in bile reflux and acid secretion, which may inhibit *H. pylori* growth in the residual stomach.[18–21] The possibility of dynamic changes raises the question for clinicians regarding the need for "reinvestigation of *H. pylori* infection in the application of postoperative *H. pylori* eradication.

Therefore, we conducted a large-scale, multicenter, prospective cohort study to evaluate the postoperative changes in *H. pylori* detection and to analyze the factors influencing dynamic changes in *H. pylori* detection after distal or proximal gastrectomy for GC.

2 | METHODS

2.1 | Study design

This prospective multicenter cohort study was conducted by enrolling patients from 22 institutions belonging to the Clinical Study Group of the Osaka University Upper Gastrointestinal Group.

The eligibility criteria were as follows: (i) patients planned to undergo R0 gastrectomy (distal or proximal gastrectomy) for histologically proven primary GC with no clinical distant metastasis, and (ii) age >20 years at enrollment. The exclusion criterion was a history of gastrectomy. All the patients provided written informed consent and were enrolled preoperatively. The final extent of gastric resection depended on the intraoperative judgment of the attending surgeons in clinical practice. Reconstruction methods after gastrectomy were not specified. Gastrectomy was performed using either open laparotomy or laparoscopy.

Data on patient characteristics, including history of *H. pylori* eradication, clinical features, surgical outcomes, and postoperative findings, were prospectively reviewed. The cancer stage was described according to the 3rd English edition of the Japanese Classification of Gastric Carcinoma.[22]

The study protocol was approved by the Institutional Review Board of each participating hospital and the study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CR) of Japan (identification number: UMIN 000020280).

2.2 | *H. pylori* test and follow-up

All patients were tested using one method for *H. pylori* preoperatively. All established *H. pylori* infection tests, including a blood test measuring antibodies to *H. pylori*, rapid urease test, histopathology test, urea breath test, stool antigen test, and culture method were permitted. They were instructed to discontinue PPI medication for 2 weeks before the *H. pylori* test. Patients for *H. pylori* positive was inhibited to the eradiation after surgery for 1 year and tested again by any method 1 year after surgery. Blood test measuring antibodies may take more than 1 year to become negative after successful eradication, so we recommended not to use this method.

2.3 | Study endpoints

The primary endpoint was the spontaneous eradication rate of *H. pylori* 1 year after surgery. The secondary endpoints were the prevalence of *H. pylori* infection in patients who underwent distal or proximal gastrectomy, overall survival, and relapse-free survival. The spontaneous eradication of *H. pylori* was defined as cases in which patients who had a positive test before surgery, regardless of preoperative eradication history, had a negative test A1 year after surgery. The prevalence of *H. pylori* infection was calculated considering all patients with a history of eradication as positive, regardless of the results of *H. pylori* tests.

2.4 | Statistical analysis

All statistical analyses were performed using JMP software version 17.0 (SAS Institute Inc., Cary, NC, USA). The demographic and

clinicopathological characteristics of the patients were summarized descriptively. All quantitative values were expressed as means and standard deviations, unless otherwise stated. Student's *t*-tests or Mann–Whitney *U* tests and Pearson's χ^2 tests were used to compare continuous and categorical variables, respectively. All values were two-tailed, and *p*-values <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Baseline demographics

A flowchart of the study is presented in Figure 1. We enrolled 1265 patients with histologically confirmed GC between February 2016 and November 2017. Eighteen patients were excluded due to non-adenocarcinoma histology ($n=11$) and no examination for preoperative *H. pylori* infection ($n=7$). A total of 1247 patients were included in this study. The baseline characteristics of the patients are summarized in Table 1. The preoperative *H. pylori* test results were positive in 756 patients and negative in 491 patients. We showed the comparison of methods for diagnosis of preoperative *H. pylori* infection in Table 2. There showed no difference in the positive rate depending on the measurement method. Seventy-nine of the patients with a negative *H. pylori* test had a history of eradication therapy, so the prevalence of *H. pylori* infection was 67.0% (835 patients). Distal gastrectomy was performed in 938 patients, whereas proximal gastrectomy was performed in 105 patients, and total gastrectomy in 193 patients. Among the patients in this study, 94.8% received antibiotics exclusively on the day of their surgery.

The preoperative *H. pylori* infections according to patient characteristics and initial disease status are shown in Table 3. *H. pylori* infection rates were higher in females, younger patients (<70 years), those with middle or lower gastric lesions, and those with undifferentiated histological classification.

3.2 | *H. pylori* infection status of the patients 1 year after surgery

Of the 614 patients who presented positive preoperative *H. pylori* tests and underwent distal or proximal gastrectomy, *H. pylori* status 1 year after surgery was assessed in 541 cases, excluding 22 undiagnosed and 51 lost to follow-up cases. Two hundred and eighty-five patients became negative for *H. pylori* infection, and the spontaneous eradication rate was 52.7% (95% confidence interval 48.5–56.8). By the comparison of methods for diagnosis of postoperative *H. pylori* infection, there showed no difference in the positive rate depending on the measurement method (Table 4).

In Table 5 we analyze the factors associated with *H. pylori* spontaneous eradiation after gastrectomy. Male sex and older age (>70 years) were significantly associated with the *H. pylori* spontaneous eradiation rate, whereas surgical procedure (proximal or distal gastrectomy), type of reconstruction, presence of adjuvant therapy, and histological type of the tumor were not significantly associated with spontaneous eradication.

4 | DISCUSSION

Whether *H. pylori* eradication is effective in preventing GC after gastrectomy remains controversial.[8,23] However, most guidelines consider GC as an indication for *H. pylori* eradication based on reports of metachronous cancer prevention.[10,11,23] The impact of partial gastrectomy on *H. pylori* infection status has not been fully evaluated, although several reports from a small number of patients suggest that *H. pylori* spontaneously regresses after the procedure.[16,19] Previous studies have shown that the conversion rate for *H. pylori* negative conversion was approximately 40%[17,21,24]; however, those were small, retrospective studies. The present study is the first multicenter, prospective, large cohort study to focus on the spontaneous eradication of *H. pylori* infection after gastrectomy for GC. In this

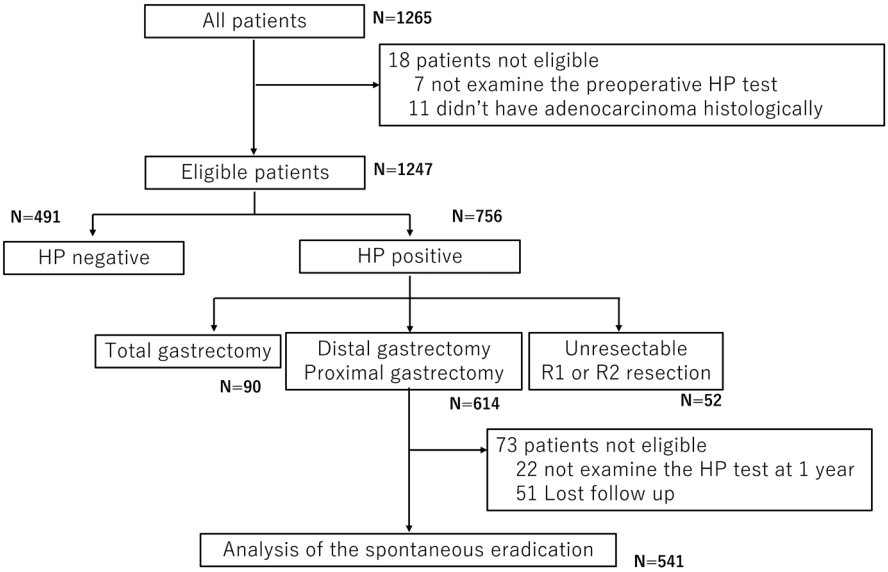

FIGURE 1 Flow chart of the study recruitment.

TABLE 1 Baseline characteristics of the 1247 patients.

	Value
Age, years	71 (23–92)
Sex	
Male	834 (66.9%)
Female	413 (33.1%)
Tumor histology	
Differentiated	710 (56.9%)
Undifferentiated	537 (43.1%)
Preoperative *H. pylori* test	
Positive	756 (61.6%)
Negative	491 (39.4%)
H. pylori eradication history	79 (6.3%)
Location	
U	219 (17.6%)
M	524 (42.0%)
L	504 (40.4%)
Type of gastrectomy	
Distal gastrectomy	934 (74.9%)
Billroth I	642 (51.5%)
Billroth II	6 (0.5%)
Roux-en-Y	298 (23.9%)
Proximal gastrectomy	102 (8.2%)
Total gastrectomy	191 (15.3%)

Note: Data are presented as median (range) or numbers (%).
Abbreviations: L, lower portion of the stomach; M, middle portion of the stomach; U, upper portion of the stomach.

TABLE 2 Comparison of methods for diagnosis of preoperative *H. pylori* infection status.

	Positive	Negative
Blood test (Antibody)	667 (60.4%)	438 (39.6%)
Rapid urease test	49 (65.3%)	26 (34.7%)
Histopathology	22 (66.7%)	11 (33.3%)
Urea breath test	9 (56.3%)	7 (43.8%)
Stool antigen test	4 (36.4%)	7 (63.6%)
Culture method	5 (71.4%)	2 (28.6%)

Note: Data are presented as numbers (%).

study, 835 (67%) of the 1247 patients with GC enrolled presented *H. pylori* infection before surgery. Approximately half (52.7%) of the patients who were not treated with bactericidal therapy after distal or proximal gastrectomy spontaneously became negative for *H. pylori* 1 year after surgery, which was a relatively higher rate than those reported in previous studies.[17,21,24] Based on these results, early eradication therapy for *H. pylori* may not be required, and eradication treatment could be administered solely for patients who test positive for *H. pylori* infection 1 year after surgery.

Some studies have analyzed factors related to the spontaneous eradication of *H. pylori*.[17–19] While the rate of *H. pylori* infection is

TABLE 3 Preoperative *H. pylori* infection status according to the characteristics of the patients and initial disease ($N = 1247$).

	Positive ($N = 835$)	Negative ($N = 412$)	*p* Value
Age, years			
<70	401 (72.4%)	153 (27.6%)	>0.001
≥70	434 (62.6%)	259 (37.4%)	
Sex			
Male	537 (64.4%)	297 (35.6%)	0.006
Female	298 (72.2%)	115 (27.9%)	
Location			
U	132 (60.3%)	87 (39.7%)	0.020
M/L	703 (68.4%)	325 (36.2%)	
Stage			
I/II/III/IV	458/167/156/54	197/94/79/42	0.062
Type of histology			
Differentiated	453 (63.8%)	257 (41.8%)	0.006
Undifferentiated	382 (71.1%)	155 (28.9%)	

Note: Data are presented as numbers (%).
Abbreviations: L, lower portion of the stomach; M, middle portion of the stomach; U, upper portion of the stomach.

TABLE 4 Comparison of methods for diagnosis of postoperative *H. pylori* infection status.

	Positive	Negative
Blood test (Antibody)	81 (57.0%)	61 (43.0%)
Rapid urease test	50 (44.2%)	63 (55.8%)
Histopathology	3 (33.3%)	6 (66.7%)
Urea breath test	39 (52.7%)	35 (47.3%)
Stool antigen test	79 (41.8%)	110 (58.2%)
Culture method	3 (23.1%)	10 (76.9%)

Note: Data are presented as numbers (%).

higher in patients who undergo reconstructive surgery with minimal bile reflux, it is lower in those who undergo reconstructive surgery with bile reflux.[25–27] Fukuhara et al. speculated that the spontaneous eradication of *H. pylori* might be related to the reconstruction method employed after distal gastrectomy as the *H. pylori* prevalence in their study was 76.9%, 71.4%, and 40% after the Roux-Y, B-I, and B-II techniques, respectively.[28] Because bile regurgitation is more severe in the residual stomach after the B-II than after the Roux-Y and B-I methods, such a factor may be responsible for the associated lower rate of *H. pylori* infection. However, in the present study, the number of patients who underwent the B-II reconstruction method was too small to allow comparison; nonetheless, we confirmed the similarity between the Roux-Y and B-I techniques, as previously reported. Furthermore, gastrectomy type (distal or proximal) was not associated with *H. pylori* eradication. Thus, gastrectomy itself, rather than bile reflux or the site of the resected gastric lesion, might influence *H. pylori* eradication against our expectations. Additionally, while the rate of spontaneous eradication of *H. pylori* in the present

TABLE 5 Spontaneous *H. pylori* eradication according to the characteristics of the patients.

	Negative conversion ($N=285$)	Persistently positive ($N=256$)	*p* Value
Age, years			
<70	130 (46.7%)	149 (53.4%)	0.003
≥70	155 (59.2%)	107 (40.8%)	
Sex			
Male	193 (56.9%)	146 (43.1%)	0.013
Female	92 (45.5%)	110 (54.5%)	
Surgery			
DG	258 (52.2%)	236 (47.8%)	0.534
PG	27 (57.4%)	20 (42.6%)	
DG			
Billroth I	186 (53.3%)	163 (46.7%)	0.426
Roux-en Y	72 (49.7%)	73 (50.3%)	
PG			
EG	20 (54.1%)	17 (45.9%)	0.371
Double tract	7 (70.0%)	3 (30.0%)	
Adjuvant chemotherapy			
Yes	81 (58.3%)	58 (41.7%)	0.199
No	201 (51. %)	193 (49.0%)	
Type of histology			
Differentiated	161 (52.4%)	146 (47.6%)	0.974
Undifferentiated	124 (53.0%)	110 (47.0%)	

Note: Data are presented as numbers (%).

Abbreviations: DG, distal gastrectomy; EG, esophagogastric anastomosis; PG, proximal gastrectomy.

study was significantly higher in males and the elderly (>70 years), the relevance of nutrition and other immunity factors that could impact spontaneous eradication remain unclear.

In this study, we confirmed preoperative *H. pylori* infection in 835 (67%) patients, including 79 patients who had a history of eradication therapy. While this finding is lower than previously reported prevalence rates,[23,24] it is consistent with the recent decline in *H. pylori* infection rates. We found that *H. pylori* infected patients were younger, mostly female, and presented more frequently an undifferentiated malignancy histology. The high frequency of tumors located in the middle and lower gastric region is consistent with the literature, which reports that *H. pylori* is primarily a risk factor and more commonly associated with cancers in the middle and lower location. *H. pylori* causes chronic active inflammation of the gastric mucosa, leading to the loss of gastric glands (i.e., atrophic gastritis), which progresses to intestinal metaplasia, dysplasia, and adenocarcinoma. This may explain the reason for which GC in the middle and lower gastric regions are more commonly associated with *H. pylori*. Our results showed that *H. pylori* positivity was more frequent in undifferentiated than differentiated tumors. Although *H. pylori* is more commonly associated with the differentiated type, it has also been observed in undifferentiated GCs[29] and it has still remained unclear.

Several studies have reported the effect of *H. pylori* infection on the survival of patients with GC and an *H. pylori* negative status has been described as an independent predictor of poor prognosis in overall survival,[7,9] GC-specific survival,[8] and recurrence-free survival.[7] The better prognosis observed in patients with *H. pylori* infection is explained by an improved immune response against the tumor[7]; additionally, because *H. pylori* components mimic specific receptors or surface molecules on gastric epithelial cells, auto-antibodies could induce a cross-reaction against gastric cancer cells.[30] However, several authors have raised doubts regarding the real prognostic value of *H. pylori* status, suggesting that *H. pylori* negativity may be simply related to more advanced tumor progression.[31,32] Choi et al. reported the analysis about the influence of eradiation of *H. pylori* after subtotal gastrectomy on prognosis and reported that the benefits of overall and GC-specific survival had been observed in the *H. pylori*-eradicated group.[11] In this study, there are no difference between two groups in pathological stage and a follow-up survey will clarify the influence of *H. pylori* eradication on survival in the near future.

This study had several limitations. First, we checked *H. pylori* status by single method, which may vary in accuracy and sensitivity, and that may have influenced the results of this study. By the analysis of the comparison of methods checking preoperative status, there showed at least no difference among them. Furthermore, although we recommended not to use the blood test after surgery, 13.7% of patients were checked by the blood test. And because it

showed slightly higher positive rate, there is a possibility that our negative conversion rate is lower than the real data. Second, we examined *H. pylori* test results only at one point 1 year after gastrectomy. Some studies have suggested that spontaneous *H. pylori* eradication may be related to the time elapsed after surgery.[17] With data of *H. pylori* prevalence being 29.5%, 13.6%, and 10% at 1–15, 16–30, and >30 years postoperatively, respectively,[17] they speculated that the prevalence of *H. pylori* infection tended to decrease as the postoperative period increased. However, because early eradication is necessary to decrease carcinogenesis, the optimal timing for the confirmation of eradication and therapy for such remains unclear. Furthermore, another limitation of this study is the lack of assessment of gastric mucosal atrophy. Although *H. pylori* infection is known to induce gastric mucosal atrophy,[12,15,16] *H. pylori* is rarely found in atrophic mucosa. Therefore, it is important to investigate the association between *H. pylori* eradication and gastric mucosal atrophy in both pre- and postoperative endoscopic findings. However, the assessment of the degree of gastric mucosal atrophy was not performed in this multicenter study due to the difficulty of standardization among institutions. Further research is needed to address this issue.

5 | CONCLUSION

This multicenter prospective cohort study showed that 52.7% of patients experienced spontaneous eradication of *H. pylori* after partial gastrectomy, regardless of the type of surgery or method of reconstruction; such a rate is relatively high compared to other studies. Therefore, we believe that the strategy of 1-year postoperative follow-up with *H. pylori* testing is mandatory for eradication therapy for *H. pylori* positive patients.

AUTHOR CONTRIBUTIONS

Takeshi Omori: Conceptualization, methodology, writing—original draft, formal analysis, investigation, data curation, visualization. **Tsuyoshi Takahashi:** Conceptualization, methodology, formal analysis, investigation, data curation, visualization supervision, project administration. **Yukinori Kurokawa:** Conceptualization, writing review and editing. **Toru Masuzawa:** Investigation, validation. **Yusuke Akamaru:** Investigation, validation. **Masaaki Motoori:** Investigation, validation. **Takuro Saito:** Investigation, validation. **Kazuyoshi Yamamoto:** Investigation, validation. **Kazuhiro Nishikawa:** Investigation, validation. **Hiroshi Imamura:** Investigation, validation, **Atsushi Takeno:** Writing—review and editing. **Ryohei Kawabata:** Writing—review and editing. **Yoshiyuki Fujiwara:** Conceptualization, writing—review and editing. **Hidetoshi Eguchi:** Writing—review and editing. **Yuichiro Doki:** Writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

All authors report no conflicts of interest or financial ties with any of the firms mentioned in this report. Y. Kurokawa is an Associate Editor of *Annals of Gastroenterological Surgery*. Y. Doki. is an Editorial Board member of *Annals of Gastroenterological Surgery*.

ETHICS STATEMENT

Approval of the research protocol: The study protocol was approved by the Institutional Review Board of each participating hospital.
Informed Consent: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1964 and later versions. Informed consent for inclusion in the study or equivalent was obtained from all patients.
Registry and the Registration No. of the study/trial: The study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CR) of Japan (identification number: UMIN 000020280).
Animal Studies: N/A.

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