The influence of gastrectomy for gastric cancer on the spontaneous disappearance of *Helicobacter pylori*: A single-center prospective study

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Abstract

Background: *Helicobacter pylori* (HP) eradication is recommended after endoscopic treatment of early gastric cancer (EGC). However, although cases of spontaneous resolution of HP after gastrectomy due to changes in the environment have been reported, there is no evidence for the efficacy of HP eradication in suppressing atypical carcinogenesis after gastrectomy. Herein, we prospectively studied the spontaneous disappearance rate of HP after gastrectomy in patients with gastric cancer.

Methods: From April 2016 to May 2020, 100 patients who underwent gastrectomy with preoperatively confirmed HP in the stool antigen test were tested one year after surgery in this trial. There were 20 cases of total gastrectomy (TG), 9 cases of proximal gastrectomy (PG), and 71 cases of distal gastrectomy (DG) consisting of 29 cases with Billroth-1 (B-1) reconstruction and 42 cases with Roux-en-Y (RY) reconstruction.

Results: After one year, 46 patients were positive, and 54 patients were negative for HP infection. In the univariate analysis, surgical procedure, pathological stage, and the presence of postoperative chemotherapy were significant factors for spontaneous resolution of HP infection. In multivariate analysis, only the surgical technique of TG remained as an independent factor. There were no significant differences in the rates of HP resolution between B-1 and RY reconstruction.

Conclusions: One year after gastrectomy, spontaneous disappearance of HP was observed in approximately half of the patients. Therefore, HP eradication in patients with gastric cancer in the early postoperative period is not necessary, even if they are preoperatively positive for HP infection.

Trial registration: Registration number: University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN ID: UMIN000046614); Registration date: 12/01/2022, retrospectively registered.

Background

Helicobacter pylori (HP) is a major cause of gastric carcinogenesis and is associated with an increased risk of chronic gastritis, atrophic gastritis, peptic ulcer disease, intestinal metaplasia, dysplasia, and subsequently of gastric cancer (GC) or mucosa-associated lymphoid tissue (MALT) lymphoma. The mechanism of HP-induced GC includes HP-induced atrophic gastritis and intestinal metaplasia, epithelial mesenchymal transition, and generation of GC stem cells [1,2]. A series of randomized control and cohort studies suggested the value of HP eradication for the prevention of GC and MALT lymphoma or other benign diseases [3]. It is widely accepted that HP eradication reduces the recurrence of tumors or metachronous cancers and improves survival in patients who undergo endoscopic resection for early GC (EGC) [2-5]. Therefore, HP eradication is widely recommended in most guidelines for patients who undergo endoscopic resection for EGC.

Although there are some reports of HP eradication after gastrectomy, including EGC and advanced GC (AGC) [6,7], there are no reports on the natural history of HP after gastrectomy. The aim of this trial was to

evaluate the status of postoperative HP infection in our hospital in patients with preoperative HP infection.

Methods

Patients

The aim of this single-center prospective trial was to evaluate the status of postoperative HP infection in our hospital in patients with preoperative HP infection. From April 2016 to May 2020, 378 patients were diagnosed with GC by esophagogastroduodenoscopy in accordance with the Union for International Cancer Control (UICC) tumor node metastasis (TNM) classification and underwent surgical treatment in our hospital. The 116 patients were positive for HP before surgery, and 112 patients agreed to participation in this prospective trial, wherein they had no eradication of HP after surgery and were retested for the presence of HP antigen in the stool after one year. Of these, 1 patient died of GC, 1 patient died of other disease, 1 patient received eradication of HP at another institution, 7 patients were converted to another institution and 2 patients had no attending our hospital. These 12 patients were excluded from this trial (Figure 1).

Surgical procedure

We performed TG with Roux-en-Y (RY) reconstruction, proximal gastrectomy (PG) with the double flap technique, distal gastrectomy (DG) with Billroth-1 (B-1) reconstruction, or RY reconstruction. In cases of DG, we selected B-1 reconstruction as far as possible.

HP status evaluation

The stool antigen test (SAT) is a noninvasive method with good sensitivity and specificity of 94% and 97%, respectively, for the diagnosis of HP infection [8]. All eligible patients underwent pre- and post-operative HP SATs by enzyme immunoassay (EIA) using the TESTMATE Pylori Antigen EIA^R (Wakamoto Pharmaceutical Co., Japan).

Statistical analysis

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphic user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [9].

The Student's t-test and chi-square test were used to compare the baseline characteristics between the HP-positive and HP-negative groups. To assess the factors related to postoperative HP status, we performed the Student's t-test and multivariate logistic regression analysis of independent risk factors. Statistical significance was set at $p < 0.05$.

Results

A total of 378 patients were diagnosed with GC in accordance with the Union for UICC TNM classification in our hospital. Preoperatively, 116 patients were positive for HP infection and 185 patients were negative. The remaining 11 patients were eradicated, and 66 were not examined. Data from a total of 100 patients were collected according to the CONSORT diagram of this prospective trial (Figure 1).

In the first postoperative year, 46 patients tested positive for HP infection, and 54 patients were negative. Patient characteristics and the results of the univariate analysis are shown in Table 1. There were no differences in age at surgery, sex, surgical approach, histological characteristics of the tumor, history of smoking, history of alcohol consumption, presence of preoperative atrophic gastritis, use of proton pump inhibitors during the first year after surgery, and antibiotic use during the first year after surgery (treatment other than for the purpose of HP eradication). By contrast, there were statistically significant differences in surgical procedure, pathological stage, and chemotherapy during the first year after surgery between the two groups (Table 1). As shown in Table 2, only the surgical procedure was identified as an independent factor in the logistic regression analysis (odds ratio [OR] 2.13, 95% confidence interval [CI] 1.33-3.39, $p=0.0151$).

After excluding patients who underwent TG, a comparison of surgical procedures showed no statistically significant difference between PG and DG in the rate of spontaneous resolution of HP (Table 3a). Among patients who underwent DG, there was no statistically significant difference between those who underwent B-1 and RY reconstruction (Table 3b).

Discussion

HP is a human pathogen and its infection leads to chronic gastritis, atrophic gastritis, peptic ulcer disease, intestinal metaplasia, dysplasia, and subsequently to GC or MALT lymphoma [1,2]. Thus, screening and eradication of HP are recommended in many guidelines. A randomized controlled study of EGC patients undergoing endoscopic resection reported that HP eradication reduces the incidence of metachronous GC or gastric neoplasia [2-5]. However, one prospective study of eradication of HP after gastrectomy reported that atrophic gastritis and intestinal metaplasia were associated with spontaneous disappearance of HP [10]. Some retrospective studies have reported that HP eradication after gastrectomy influences long-term prognosis, but no consensus has been reached [4-7,11,12]. In addition, previous reports did not consider the possibility of spontaneous disappearance of HP after gastrectomy.

Thus, we considered the possibility of spontaneous disappearance of HP and prospectively studied patients with preoperative HP infection after gastrectomy that did not undergo postoperative HP eradication. Of the 100 patients in this trial, 46 patients tested positive and 54 patients tested negative for HP infection at one year after surgery. In univariate analysis, surgical procedure, histopathological stage, and postoperative chemotherapy were statistically significant (Table 1). In multivariate analysis, only the surgical procedure (mainly TG) was found to be an independent factor (Table 2). However, the fact that

all patients who underwent TG tested negative for HP infection may have contributed to the significant difference. To the best of our knowledge, this is the first study to indicate that HP cannot survive elsewhere in the gastrointestinal tract other than the stomach and indicate the complete disappearance of HP after TG.

We also compared the groups according to the surgical procedure after excluding TG cases and found no difference between PG and DG (Table 3a). In 71 cases of DG, there was no statistically significant difference between B-1 and RY reconstruction (Table 3b).

In general, the changes in postoperative HP infection status have been suggested to be related to bile reflux and dramatic changes in acid secretion after gastrectomy, which appear to inhibit the growth of HP in the remnant stomach. A previous study reported that the spontaneous clearance rate of HP is related to the type of surgery. Billroth-2 (B-2) reconstruction had a higher bile reflux rate than B-1 reconstruction [1,13]; therefore, RY reconstruction is preferable when B-1 reconstruction is difficult. Antrectomy largely removes the gastrin-cell population, which suppresses acid production and subsequently affects HP colonization in the residual stomach. Decreased acid levels could promote the growth of gastric or duodenal organisms [11]. There was a tendency for more bile reflux in B-1 reconstruction and smaller remnant stomach in RY reconstruction, and we investigated how this might be related to the spontaneous disappearance of HP. However, the results showed no statistical difference between B-1 and RY reconstruction in the rate of spontaneous clearance of HP. Furthermore, this is the first report comparing B-1 and RY reconstruction for the spontaneous disappearance of HP. The double flap technique was performed in 9 patients with PG, and spontaneous resolution of HP was observed in four patients. Therefore, factors other than the condition of the remaining stomach, such as bile reflux and hyposecretion of gastric acid, may be involved in the mechanism of HP disappearance. To the best of our knowledge, there is no evidence of an association between PG and HP status. In addition, among the 46 patients that tested positive one year after gastrectomy, 11 patients were also tested three years after surgery, and 3 patients tested negative for HP without eradication. Therefore, patients with positive HP status one year after gastrectomy also have a high rate of positivity at three years after gastrectomy, suggesting that if the HP does not disappear spontaneously in the first postoperative year, the rate of HP spontaneous disappearance is low even in the long term.

In recent years, adverse effects of HP eradication have also been reported. HP eradication regimens consist of a combination of broad-spectrum antibiotics, including amoxicillin, clarithromycin, tetracycline, or metronidazole. Antibiotic treatment disrupts the gut microbiota, which affects various steps in the process of carcinogenesis. The UK medical records database reported a possible association between repeated macrolide antibiotic use and increased risk of various types of cancer [14]. Clarithromycin has been reported to be associated with increased cardiovascular mortality risk, especially in the short-term after the initiation of treatment [15]. In addition, a prospective randomized trial found that 2 weeks of clarithromycin treatment significantly increased long-term overall mortality over a 10-year follow-up period [16]. In terms of HP eradication rates, Lin et al. summarized previous reports showing no difference

between pre- and post-gastrectomy; therefore, eradication of HP could not be improved after gastrectomy [17].

Given the adverse effects of HP eradication and the results of our trial, early HP eradication after gastrectomy should be avoided and eradication should be considered one year after gastrectomy.

Recently, it has been reported that chemotherapy for non-hematological malignancies affects the composition of the gut microbiota during myelosuppression [18]. However, we found no statistically significant difference in HP disappearance between patients with and without postoperative chemotherapy. Nevertheless, the rate of HP disappearance was higher in the postoperative chemotherapy group (Tables 1 and 2), suggesting that chemotherapy for GC may have influenced the disappearance of HP. Larger trials are warranted to confirm whether a statistically significant difference exists.

This trial has some limitations worth noting including its single-center design and relatively small number of patients. Although we were not able to elucidate the mechanism of the spontaneous disappearance of HP, we believe that the results are valuable as this is a rare prospective investigation of HP infection status in patients who underwent gastrectomy without HP eradication. Taken together, our results and those of previous studies suggest that it is not necessary to eradicate HP in the early period after gastrectomy, because about half of the cases disappear spontaneously within one year after surgery, regardless of the surgical procedure or type of reconstruction. Therefore, early postoperative eradication of HP may not always be necessary but should be considered in patients with persistent HP infection at one year after gastrectomy.

Conclusions

Early postoperative eradication of HP may not always be necessary, and if the patient is still infected with HP one year after gastrectomy, eradication should be considered.

Abbreviations

AGC	Advanced gastric cancer
DG	Distal gastrectomy
EGC	Early gastric cancer
GC	Gastric cancer
HP	Helicobacter pylori
MALT	Mucosa-associated lymphoid tissue
PG	Proximal gastrectomy

PPI	Proton pump inhibitor
SAT	Stool antigen test
TG	Total gastrectomy
TNM	Tumor node metastasis
UICC	Union for International Cancer Control

Declarations

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent to be included in the study, or the equivalent, was obtained from all patients. This trial was approved by the local review board (Onomichi General Hospital ethics review committee, OJH-001551), and registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN ID: 000046614). Registration date: 12/01/2022.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

SY and NF made substantial contributions to the concept and design of the study and data acquisition and interpretation. KT, MN, and TN were involved in drafting the manuscript and critical revision for important intellectual content. NF approved the final version of the manuscript submitted for publication. All authors read and approved the final manuscript.

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Tables

Table 1 to 3 is available in the Supplemental Files section.

Figures

Figure 1

CONSORT diagram for the trial.

Supplementary Files

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