

Hoon Jai Chun, MD, PhD, AGAF, Professor, Series Editor

## ***Helicobacter pylori* infection following partial gastrectomy for gastric cancer**

Sanghoon Park, Hoon Jai Chun

Sanghoon Park, Department of Internal Medicine, KEPKO Medical Center, Seoul 132-703, South Korea

Hoon Jai Chun, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Institute of Digestive Disease and Nutrition, Korea University College of Medicine, Korea University Medical Center, Seoul 136-705, South Korea

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Correspondence to: Hoon Jai Chun, MD, PhD, Professor, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Institute of Digestive Disease and Nutrition, Korea University College of Medicine, Korea University Medical Center, Incheon-ro 73, Seongbuk-gu, Seoul 136-705, South Korea. drchunhj@chol.com

Telephone: +82-2-9205699 Fax: +82-2-9531943

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### **Abstract**

Gastric remnants are an inevitable consequence of partial gastrectomy following resection for gastric cancer. The presence of gastric stumps is itself a risk factor for redevelopment of gastric cancer. *Helicobacter pylori* (*H. pylori*) infection is also a well-known characteristic of gastric carcinogenesis. *H. pylori* colonization in the remnant stomach therefore draws special interest from clinicians in terms of stomach cancer development and pathogenesis; however, the *H. pylori*-infected gastric remnant is quite different from the intact organ in several aspects and researchers have expressed conflicting opinions with respect to its role in pathogenesis. For instance, *H. pylori* infection of the gastric stump produced controversial results in several recent studies. The prevalence of *H. pylori* infection in the gastric stump has varied among recent reports. Gastritis developing in the remnant stomach presents with a unique pattern of inflammation that is different from the pattern seen in ordinary gastritis of the intact organ. Bile

refluxate also has a significant influence on the colonization of the stomach stump, with several studies reporting mixed results as well. In contrast, the elimination of *H. pylori* from the gastric stump has shown a dramatic impact on eradication rate. *H. pylori* elimination is recognized to be important for cancer prevention and considerable agreement of opinion is seen among researchers. To overcome the current discrepancies in the literature regarding the role of *H. pylori* in the gastric stump, further research is required.

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**Key words:** *Helicobacter pylori*; Gastrectomy; Gastric cancer

**Core tip:** *Helicobacter pylori* (*H. pylori*) are colonizing the remnant stomach after partial gastrectomy for gastric cancer interacts with the remaining gastric stump in a unique way. Many theories have been proposed as to the exact role or etiological manifestation of *H. pylori* on the remnant stomach relating to prevalence rate, carcinogenesis, and extent of clearance. Yet, studies have provided inconsistent results and no unified opinion has been reached on each topic. This article summarizes findings from the collective investigational reports on the influence of *H. pylori* in the gastric remnant.

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### **INTRODUCTION**

Curative attempts to resect gastric adenocarcinoma leave

**Table 1** Differences in the characteristics and manifestations of different gastric resections recently presented

Manifestations	Distal gastrectomy	Proximal gastrectomy
Bile reflux	↑	↓
Polymorphonuclear infiltration (i.e., rate of inflammation)	↑ (60.5%)	↓ (12.9%)
<i>H. pylori</i> infection rate	↑	↓
Chronic and active inflammation	↑	↓
Intestinal metaplasia	↓	↑

It is suggested that the presence of a gastric stump after proximal gastrectomy promotes the progression of intestinal metaplasia and hampers the colonization of *Helicobacter pylori* (*H. pylori*). However, this notion is contrary to results from previous studies showing a relatively low *H. pylori* prevalence in the gastric stump.

a gastric stump, creating the possibility of metachronous tumors arising from the remnant organ. A number of post-surgical management strategies have been adopted to lessen the risk of gastric malignancy recurrence, such as adjuvant chemotherapy and regular endoscopic surveillance. Based on the strong and well-established association between *Helicobacter pylori* (*H. pylori*) and carcinogenesis in intact stomach, identifying and eradicating the presence of this bacterial carcinogen has been suggested as another approach for decreasing cancer recurrence in the gastric stump<sup>[1,2]</sup>. However, some researchers have refuted the evidentiary importance of this strategy, since the carcinogenic role of *H. pylori* has yet to be definitively established in remnant stomach<sup>[3]</sup>.

Following surgical resection, remnant tissue provides a unique environment for the propagation of *H. pylori* as compared to the intact stomach. The natural course of *H. pylori* infection is typified by atrophic changes that result from microorganisms that migrate to the proximal stomach. The role of *H. pylori* infection in subjects who undergo distal gastrectomy for gastric cancer has been unclear due to mixed results from recent studies. In this article, we will review the research on the interaction between *H. pylori* and its anatomically altered habitat. We will further explore the role of bile refluxate on *H. pylori* infection, and the effect of *H. pylori* eradication on the progression of gastric carcinogenesis.

## OBSERVATIONS OF *H. PYLORI* INFECTION IN THE REMNANT STOMACH

### Prevalence of *H. pylori* infection after partial gastric resection

Several clinical conditions confer a high risk for gastric cancer. These conditions include pan-gastritis, prior gastric neoplasia, and corpus-dominant gastritis. Among clinical considerations, previous gastric procedures are considered to be an indication for aggressive *H. pylori* eradication<sup>[3,4]</sup>. According to guidelines from the Maastricht IV/Florence Consensus Report, eradication of *H. pylori* is strongly recommended as an essential treatment

for the prevention of gastric cancer in populations at high risk<sup>[1]</sup>.

The reported rates of *H. pylori* infection in the remnant stomach after distal gastrectomy fall within a broad range (19%-70%)<sup>[5-9]</sup>. Data from one group of researchers concluded that *H. pylori* prevalence is relatively low in patients who have undergone distal gastrectomy<sup>[10,11]</sup>. Another study from Israel supports this data with demonstrated infection rates as low as 18%<sup>[12]</sup>. This low prevalence of *H. pylori* after distal gastrectomy is explained by the decreased survivability of the microorganism in patients with an absent antrum. The antrum serves as the main colonizing location for *H. pylori*, as well as the source of bile reflux that produces an increase in intra-gastric pH<sup>[13,14]</sup>. Some researchers have suggested that the elevation in pH in the stomach leads to a reduction or disappearance of *H. pylori* in the gastric stump; furthermore, the organism is detected more commonly in the gastric corpus than near the anastomotic rim<sup>[7,15]</sup>. Biliary reflux from the small intestine to the stomach after the removal of the pyloric sphincter is suspected to further inhibit *H. pylori* proliferation<sup>[16-18]</sup>. Some studies have suggested that bile inhibits *H. pylori* growth *in vitro* and may play a role in eradicating *H. pylori in vivo*<sup>[14,19]</sup>. The type of anastomosis utilized during surgical resection is also known to influence the rate of *H. pylori* infection (Table 1). Several investigations have suggested that bile reflux in conjunction with the type of anastomosis used for the procedure inhibits *H. pylori* colonization<sup>[20,21]</sup>.

### *H. pylori* mediated gastritis of the gastric stump

*H. pylori* infection in the gastric remnant after gastrectomy is known to be associated with a pattern of gastritis that is characterized by active and chronic inflammatory cell infiltration into the lamina propria<sup>[11,22]</sup>. Data has suggested that the presence of *H. pylori* infection mediates the severity of inflammatory change seen in the remnant stomach<sup>[23,24]</sup>. In a study utilizing a fiberoptic detector of bilirubin, refluxate from gastrectomy subjects and endoscopic biopsy specimens were analyzed. The results suggest that mucosal erythema was induced by bile refluxate and the active chronic inflammatory cell infiltration was caused by *H. pylori* infection<sup>[11]</sup>.

The presentation of inflammation is dependent on the surgical type of gastric excision. One recent single-site investigation revealed that neutrophilic infiltration predominated in the gastric remnant of distal gastrectomy subjects but not in the remnants of proximal gastrectomy patients (Table 1, 60.5% vs 12.9%,  $P < 0.001$ )<sup>[25]</sup>. The authors explained this finding by suggesting that the gastric stump remaining after proximal gastrectomy was prone to intestinal metaplasia with continuing inflammation, creating a difficult environment for *H. pylori* colonization.

There are several factors that may influence the infection rate of *H. pylori* in the gastric stump. Early research failed to yield sufficient data comparing different types of surgery, such as the Billroth versus Roux-en-Y procedures. More recent investigations, however, have revealed

**Table 2** Some issues disputed among researchers regarding *Helicobacter pylori* infection in the gastric remnant after partial gastrectomy

Issues	Prospective	Consequence
<i>H. pylori</i> infection decreases after partial gastrectomy, depending upon surgery and anastomosis type	Distal gastrectomy leads to bile reflux and resultant elevated intra-gastric pH, hampering <i>H. pylori</i> inhabitation; this was also shown in an in vitro study <sup>[19]</sup> Billroth type II anastomosis has higher bile reflux compared with Billroth type I or vagotomy, with concordant lower <i>H. pylori</i> infection prevalence <sup>[6,8]</sup> Bile refluxate is toxic to <i>H. pylori</i> , leading to spontaneous eradication <sup>[23]</sup>	Subjects with proximal gastrectomy are prone to intestinal metaplasia, which is a difficult environment for <i>H. pylori</i> survival <sup>[25]</sup> Duodenogastric reflux "facilitates" the survival of <i>H. pylori</i> <sup>[27]</sup>
<i>H. pylori</i> is a risk factor of carcinogenesis in the gastric stump	Some academic gastroenterological societies recognize <i>H. pylori</i> as a risk factor equivalent to the intact organ <sup>[1,2]</sup>	Showing a rather low <i>H. pylori</i> infection rate suggests a different pathogenesis of gastric cancer from the remnant stomach <sup>[3]</sup>
<i>H. pylori</i> eradication is required	<i>H. pylori</i> -positive subjects with a remnant stomach after gastrectomy for cancer showed a higher prevalence for premalignant lesions compared to <i>H. pylori</i> -negative subjects <i>H. pylori</i> eradication is strongly recommended <sup>[1]</sup>	Eradication therapy improved intestinal metaplasia, preventing premalignant changes <sup>[30]</sup> Some academic gastroenterological societies do not advocate <i>H. pylori</i> eradication in the gastric stump
Bile reflux inhibits <i>H. pylori</i> inhabitation in the gastric stump	Spontaneous eradication by the reflux of bile contents is suggested <sup>[23]</sup>	There was no apparent inverse relationship between the quantity of bile refluxate and <i>H. pylori</i> infection <sup>[11]</sup> Pylorus-preserving gastrectomy led to the spontaneous clearance of <i>H. pylori</i> <sup>[28]</sup>

*H. pylori*: *Helicobacter pylori*.

that the type of gastrectomy may influence the rate of infection; that is, the *H. pylori* infection rate differed according to the type of surgery conducted. A systematic review of 36 studies that assessed *H. pylori* infection after several types of surgery for peptic ulceration showed a mean infection rate of about 50% (ranging from 19% to 73%) in patients who underwent partial gastrectomy and a relatively higher infection rate (about 83%) in subjects who underwent vagotomy procedures<sup>[8]</sup>. Another study addressed the difference in *H. pylori* infection rates in different types of anastomoses after distal gastrectomy (Billroth I or II). The Billroth type I anastomoses had an infection rate of 70.8%, significantly higher than that of the type II anastomoses (45.9%)<sup>[6]</sup>. Similarly, Billroth type II anastomoses showed significantly higher bile reflux compared with other surgical procedures such as pylorus-preserving gastrectomy or Roux-en-Y methods<sup>[10]</sup>.

Infection rates also differed between proximal and distal gastrectomy procedures. It was postulated that the remnant stomach after proximal gastrectomy was prone to intestinal metaplasia, an irreversible change that made it difficult for *H. pylori* to thrive. In the case of distal gastrectomy, which is currently a more common procedure among gastric cancer patients, bile reflux is known to influence the biologic surroundings of *H. pylori* in the stomach (Table 2).

Beyond the surgical approach employed, several additional factors have been studied with regard to the infection rate of *H. pylori*. One investigation found that the prevalence of *H. pylori* in the gastric stump was significantly decreased with the patients' age, time post-gastrectomy, and presence of severe reflux gastritis<sup>[23]</sup>. Bair *et al*<sup>[17]</sup> presented an analogous report showing that spontaneous *H. pylori* clearance was related to the type of

surgery and time of post-operative resection.

### **Influence of bile reflux: Friend or foe?**

There has been a debate regarding the exact role of bile reflux on *H. pylori* colonization in the remnant stomach after partial gastrectomy. One study demonstrated that bile reflux induces glandular atrophy and chronic inflammation but does not increase polymorphonuclear cell activity<sup>[10]</sup>. Investigations utilizing a precise bile reflux measurement described no apparent inverse relationship between the quantity of bile refluxate and *H. pylori* infection<sup>[11]</sup>. According to a study by Onoda *et al*<sup>[23]</sup>, the prevalence of *H. pylori* infection was lower in Billroth-II reconstruction patients with severe bile reflux and subsequent stomal gastritis, suggesting a spontaneous eradication of *H. pylori* by the reflux of bile contents.

In contrast, some investigators have questioned the theory of biliary obliteration of *H. pylori* in the gastric stump. One study showed that Roux-en-Y reconstruction after distal gastrectomy produces smaller amounts of bile reflux and as a result had a lower rate of *H. pylori* infection<sup>[26]</sup>. This study also observed a lower fasting enterogastric reflux in the patients who received the Roux-en-Y method (5.3%) compared with those who received Billroth II reconstruction (62.1%), as measured by biliary scintigraphy. Nakagawara *et al*<sup>[27]</sup> reported that bile refluxate facilitated the survival of *H. pylori*, speculating that *H. pylori* was perhaps inhibited by other bacteria in the gut. Pylorus-preserving gastrectomy for gastric cancer also resulted in significantly lower *H. pylori* prevalence after surgery<sup>[28]</sup>.

To date, the rate of *H. pylori* infection in the gastric remnant seems to be smaller than the rates in the anatomically intact organ. These results, however, lack a



thorough explanation of the precise mechanism providing for low *H. pylori* prevalence in the stump, and thus further investigation is required.

### Requirement for *H. pylori* eradication therapy

*H. pylori* infection in the remnant stomach after partial gastrectomy is a causative factor in gastric cancer in the residual organ<sup>[22]</sup>. Remnant stomachs that are infected with *H. pylori* after partial gastrectomy for gastric cancer are prone to develop premalignant lesions and subsequent gastric cancer<sup>[23,29]</sup>. Giuliani *et al.*<sup>[29]</sup> studied the manifestations of gastric cancer precursor lesions, such as chronic atrophic gastritis, intestinal metaplasia and dysplasia, among *H. pylori*-positive subjects. These patients had gastric remnants after gastrectomy for peptic ulcer disease or gastric cancer. *H. pylori*-positive subjects with a remnant stomach after gastrectomy showed a higher prevalence of premalignant lesions compared with *H. pylori*-negative subjects (OR = 4.20, 95%CI: 1.10-15.96). These results indicate a significant role of *H. pylori* infection in the pathogenesis of disease. The authors concluded that *H. pylori* eradication might prevent metachronous gastric cancer in subjects with higher risk after gastrectomy.

There have been mixed results regarding the efficacy of *H. pylori* eradication on the prevention of premalignant changes in the gastric mucosa such as intestinal metaplasia. In one study, standard proton pump inhibitor-based eradication therapy resulted in significant atrophic glandular improvement<sup>[50]</sup>. However, some investigators have presented the opposite result, where atrophic glands and intestinal metaplasia were not improved even after successful *H. pylori* eradication<sup>[31]</sup>. After studying the prevalence of several histological characteristics and *H. pylori* infection in subjects with gastric stumps, some researchers have concluded that *H. pylori* eradication might prevent cancer development in the remnant organ. In particular, one investigation described the spontaneous eradication of the organism in 78.8% of partial gastrectomy subjects<sup>[11]</sup>.

Methods for diagnosing the infection of remnant stomach by *H. pylori* have been another matter of discussion. In contrast to the case of an intact organ, the nature of the gastric stump after partial gastrectomy appears to affect the reliability of testing for *H. pylori* colonization. Several reports showed that urease breath test (UBT) provides lower diagnostic accuracy when using histology as a reference. From a study performed by Adamopoulos *et al.*<sup>[32]</sup> a relatively poor agreement was shown by UBT ( $\kappa$  = 0.41) in contrast to rapid urease test (RUT) ( $\kappa$  = 0.97)<sup>[32]</sup>. When UBT was compared with RUT retrospectively in another recent study, however, UBT was comparable to RUT in terms of accuracy (UBT 87% *vs* RUT 72%).

Attempts to eradicate *H. pylori* in the gastric stump show a strong success rate of around 90% across several studies<sup>[30,31]</sup>. Examining data from a study by Matsukura *et al.*<sup>[31]</sup>, *H. pylori* eradication in gastric remnants had a success rate of 70%, comparable to non-surgery patients. In

another study from Korea, the eradication rate of *H. pylori*-infected gastric stumps was 82.7%<sup>[33]</sup>. In general, with appropriate treatment, the rate of *H. pylori* eradication in the gastric stump appears to be comparable to that of intact organs.

The temporal timing of *H. pylori* eradication is an important issue to consider and has been studied by several investigators<sup>[31]</sup>. For example, surgery can be delayed for one or two weeks in order to complete *H. pylori* eradication. In addition to time considerations, bile reflux after surgery, change in gastric emptying time, type of surgery performed, perioperative antibiotic administration, and changes in intragastric pH are other factors for consideration. One randomized controlled trial concluded that pre- or post-operative *H. pylori* eradication treatment did not affect the clinical outcome in terms of eradication rate<sup>[34]</sup>. Additionally, that study found no difference among the methods for post partial gastrectomy in preventing the advance of gastric cancer. As the ordinary antibiotic selections for gastrectomy patients are generally insufficient for effective elimination, it is possible to assume that prophylactic antibiotics will not seriously affect intragastric colonization of *H. pylori*.

### Relationship between *H. pylori* and distal esophageal cancer

With respect to cancers on the distal esophagus, *H. pylori* infection is generally known to have an inhibitory role against carcinogenesis<sup>[35]</sup>. In contrast, squamous cell carcinoma in the upper or middle esophagus and adenocarcinoma adjacent to the gastro-esophageal junction is inversely related to *H. pylori* infection of stomach. Presumably, *H. pylori* colonizing the gastric stump after partial gastrectomy will influence the development of distal esophageal adenocarcinoma in some way. There is a scarcity in the literature regarding the relationship between distal esophageal cancer and the gastric remnant infected with *H. pylori*. Further investigations are needed to clarify this concern.

## CONCLUSION

*H. pylori* is a well-known etiologic factor for gastric cancer. Likewise, a remnant stomach after partial gastrectomy for gastric cancer is also an important etiological factor for gastric carcinogenesis. According to a number of studies, *H. pylori* infection in the remnant stomach seems to play a role in gastric cancer development, albeit with contrary views from various research groups. A number of questions remain, including the factors influencing the infection state, the specific eradication rate and its role in cancer development, and the exact effect of refluxed biliary contents on *H. pylori*. The prevalence of *H. pylori* in the gastric stump seems to be lower than in the intact organ, with a significant rate of elimination when therapeutically targeted for eradication. We suggest that *H. pylori* infection still needs to be eliminated from the gastric tissue to reduce the risk of stump cancer. Some researchers

propose that bile refluxate facilitates the proliferation of *H. pylori*, but most investigators advocate the inhibitory effect of bile. Overall, the presence of *H. pylori* infection in the gastric stump requires further investigation to clarify the function and role of the organism in cancer reappearance.

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