Original article

Prevalence of *Helicobacter pylori* infection in gastric remnant after distal gastrectomy for primary gastric cancer

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Abstract

Background. The development of a second primary cancer in the gastric remnant after gastrectomy for early gastric carcinoma is a problem, and eradication of *Helicobacter pylori* after the operation has been recommended. However, to date, practical indications for *H. pylori* eradication after gastric cancer surgery have not yet been reported.

Methods. We examined *H. pylori* infection in the gastric remnant after distal gastrectomy for primary gastric cancer. One hundred and nine patients who had had a gastrectomy were studied. Endoscopic findings and results from the urease test, bacteriologic assessment, serological test, and histopathological examination were analyzed.

Results. Seventy-one patients (65.1%) were judged to be positive for *H. pylori* infection. The prevalence of *H. pylori* infection was found to be significantly decreased in older patients, patients in whom the operation had been performed a long time before examination, patients with symptoms, and patients with severe reflux gastritis. On the other hand, histologically, chronic and acute gastritis correlated significantly with *H. pylori* infection. *H. pylori* prevalence was highest in mildly atrophic mucosa and decreased with more extensive atrophic changes of the mucosa.

Conclusions. The persistence of *H. pylori*-related active gastritis in the gastric remnant after gastric cancer surgery was suggested in younger patients with mild atrophic gastritis and without reflux gastritis. These patients may be the best candidates for *H. pylori* eradication therapy.

Key words *Helicobacter pylori* · Gastric remnant · Gastric cancer · Second primary cancer development

Introduction

With recent advances in the fields of diagnosis and therapy, the prognosis of gastric cancer after surgical

therapy has improved, and a long postoperative life is usual in a majority of these patients with early-stage gastric carcinoma [1]. However, in these patients, the gastric remnant (GR) retains the mucosa that had been the background of the initial cancer, and the mucosa exists in nonphysiological circumstances. Thus, the possible development of a second primary cancer in the GR has been a problem. In practice, the incidence of a second primary cancer in the GR is considerably high. At our institute, second primary cancer in the GR was found in approximately 2% of the patients after curative resection of primary gastric carcinoma [2]. Thus, post-operative endoscopic surveillance has been emphasized to detect curable early-stage cancer in the GR [3].

Our previous study demonstrated that the features of early-stage second primary cancer in the GR were somewhat different from those of ordinary primary gastric carcinoma; protruding lesions and intestinal type cancer were dominant, and the background mucosa of these lesions was often associated with atrophic gastritis or intestinal metaplasia [2,4]. Although the real cause of gastric carcinogenesis is not fully understood, several environmental factors, including infection with *Helicobacter pylori*, have been shown to be linked with gastric carcinogenesis [5]. Since Warren and Marshall [6] first isolated *H. pylori* from the stomachs of patients with gastritis, numerous studies have demonstrated the relationship between *H. pylori* infection and the development of gastric cancer [7–10]. Now, *H. pylori* is regarded as a definite carcinogen [11] and as a trigger for the sequence of carcinogenesis, because there is strong evidence for *H. pylori* infection as a cause of chronic atrophic gastritis and intestinal metaplasia, two possible precancerous lesions [9,10,12–14]. Our previous observations on the background mucosa of early-stage carcinoma of the GR also indicated an intimate association between atrophic gastritis and intestinal-type gastric carcinoma [2]. Thus, involvement of *H. pylori* in car-

cinogenesis in the GR should be considered. Eradication of *H. pylori* in the post-operative GR after gastrectomy for early-stage primary gastric carcinoma has been recommended [15]. Several studies have investigated the effect of partial gastrectomy on *H. pylori* infection [16–18]. Most of these were, however, studies of peptic ulcer patients, and to date there have been only a few small studies of *H. pylori* involvement after gastric cancer operation [19,20]. Surgery for gastric cancer differs in many ways from peptic ulcer surgery, in terms of, for example, the size of the GR, the complete devascularization and denervation because of lymph node dissection, the reconstruction method with less bile reflux, and the initial difference in background mucosa inside the stomach. Only one study has suggested the significance of *H. pylori* eradication for decreasing the risk of second primary cancer development. However, that study reported findings after endoscopic resection [21]. Thus, to date there have been no clear criteria to indicate the necessity for *H. pylori* eradication in the GR after gastric cancer surgery.

In this study, we examined *H. pylori* infection in a large number of gastrectomized patients with GR after primary gastric cancer, in an attempt to determine the significance of *H. pylori* infection after gastric cancer surgery.

Patients and methods

Patients

One hundred and nine patients (84 men and 25 women) who had had distal gastrectomy because of primary gastric cancer were studied in 1998 and 1999. The patients' ages ranged from 39 to 88 years, with an average of 63.4 years. The operations had been performed at our institute in the period 1969 to 1998. Reconstruction of the digestive tract was made either with a Billroth I type gastroduodenostomy (B-I; $n = 85$) or with a Billroth II type gastrojejunostomy (B-II; $n = 24$). Patients with noncurative resection, and those with recurrent disease within 6 months after the operation were excluded. Informed consent was obtained from all patients who participated this study.

Methods

Follow-up examination was performed by upper gastrointestinal endoscopy, and findings were graded according to the Sydney system [22]. The degree of bile reflux (–, none; +, mild; ++, severe) was also recorded [2]. At least three biopsy specimens of the gastric mucosa were sampled from both the greater curvature, 1 cm on the oral side from the anastomosis, and

the lesser curvature, 3 cm on the anal side from the esophagogastric junction. One specimen was examined by urease test, one specimen was sent for bacteriologic assessment, and the remaining specimen was fixed for histopathological examination. *H. pylori*-positivity was determined either (a) when bacteriologic assessment was positive or (b) when both the histological findings and the urease test result were positive, according to the recommendations of the Japanese Society of Gastroenterology [23].

Bacteriologic assessment. Biopsy specimens were cultured immediately, using Skirrow plates, and incubated at 37°C in an environment of 5% O₂, 10% CO₂, and 85% N₂ for 5 days. Colonies that contained Gram-negative curved organisms and that tested positive on oxidase, catalase, and urease tests, susceptibility to cephalothin, and resistance to nalidixic acid were identified as *H. pylori*-positive.

Urease test for *H. pylori*. Biopsy specimens were placed into the urease-containing well of a rapid urease test kit (Helicocheck; Otsuka Pharmaceuticals, Tokyo, Japan). A positive test result was recorded when there was a colorimetric change to red within 2 h at room temperature.

Serological test for *H. pylori*. Anti-*H. pylori* IgG antibody was detected by enzyme immunoassay (SRL, Tokyo, Japan).

Histological assessment. Biopsy specimens were fixed in 20% buffered formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin. Histopathological examination was performed according to the guidelines of the updated Sydney system [24].

Statistical methods. Statistical analyses were performed using Student's *t*-test, Fisher's exact test, and χ^2 analysis. A *P* value of less than 0.05 was considered significant.

Results

Although results obtained when *H. pylori* prevalence was judged only by the serologic test were similar to those obtained when the other criteria described in the "Materials and methods section" were followed, we adopted the results obtained from biopsied specimens. This was done because it was felt that the results obtained from biopsied specimens might demonstrate a "real-time" phenomenon more clearly than the serological test. Furthermore, by confirming *H. pylori* infection in a biopsied specimen obtained from the same portion as that used for histological assessment, accu-

Table 1. *Helicobacter pylori* infection in gastric remnant according to the characteristics of the patients and the initial disease

	<i>n</i>	<i>Helicobacter pylori</i> +	Percentage	<i>P</i> value
Sex				
Male	84	53	63.1%	NS
Female	25	18	72.0%	
Age (years)				
<50	11	11	100.0%	<0.01*
50–59	27	20	74.1%	
60–69	41	27	65.9%	
70–79	23	11	47.8%	<0.05**
80 and over	7	2	28.6%	
Stage of initial disease				
Early	73	49	67.1%	NS
Advanced	36	22	61.1%	
Histology of initial disease ^a				
Differentiated type	67	40	59.7%	NS
Undifferentiated type	41	31	75.6%	
Reconstruction method				
B-I	85	57	67.1%	NS
B-II	24	14	58.3%	
Total	109	71	65.2%	

*For each generation; **vs those aged under 70 years

NS, Not significant; B-I, Billroth I; B-II, Billroth II

^aInformation was not available for one patient **Fig. 1.** *Helicobacter pylori* (*H. pylori*) positivity according to age distribution and post-operative follow-up period

rate involvement of *H. pylori* was considered to be demonstrated.

Seventy-one patients (65.1%) were judged to be positive for *H. Pylori*. No difference was found when the patients were divided into subgroups according to sex or according to the clinicopathological features of the initial disease. The prevalence of *H. pylori* infection was 100% in patients under age 50 years, while it was only 28.6% in patients older than 80 years. As shown in Fig. 1, in the *H. pylori*-positive group, in the older patients,

there were more patients with a long follow-up period and fewer patients with a short follow-up period than in the younger patients. In the *H. pylori*-negative group also, there were more patients with a long follow-up period among the older patients than the younger ones. However, in the *H. pylori*-negative group, the percentage of patients with a short follow-up period was similar in each age category. Fifty-seven patients (67.1%) with the B-I reconstruction were *H. pylori*-positive, and 14 (58.3%) with the B-II were *H. pylori*-positive; no difference in the prevalence of *H. pylori* infection was found according to the reconstruction method (Table 1). However, when the postoperative period was considered, the prevalence of HP infection was lower in patients in whom there was a long period after operation, and a significant difference in prevalence was shown between the patients examined within 3 years after the operation (77.3%) and those examined more than 3 years after (56.9%). In B-II patients, the prevalence decreased faster than that in the B-I patients. A significant decrease in prevalence was observed between patients within and more than 3 years after the operation in B-II patients, while such a significant decrease was observed between patients within and more than 6 years after the operation in B-I patients (Table 2). More than 10 years after the initial operation, only one-fourth (3/11) of the patients were positive for *H. pylori*, regardless of the reconstruction method.

Twenty-nine patients complained of abdominal symptoms associated with post-operative status or stomal gastritis; for example, abdominal pain, fullness,

Table 2. *Helicobacter pylori* infection in gastric remnant according to length of postoperative period, and the reconstruction method

Years after operation	B-I*			B-II**			Total**		
	<i>n</i>	<i>H. pylori</i> +	Percentage	<i>n</i>	<i>H. pylori</i> +	Percentage	<i>n</i>	<i>H. pylori</i> +	Percentage
<3	33	25	75.8%	11	9	81.8%	44	34	77.3%
<6	27	19	70.4%	4	1	25.0%	31	20	64.5%
<9	14	9	64.3%	4	2	50.0%	18	11	61.1%
More than 9	11	4	36.4%	5	2	40.0%	16	6	37.5%
Total	85	57	67.1%	24	14	58.3%	109	71	65.1%

* $P = 0.05$, <6 vs 6 and over; ** $P < 0.05$, <3 vs 3 and over

Table 3. *Helicobacter pylori* infection in gastric remnant according to symptoms and endoscopic findings

	<i>n</i>	<i>H. pylori</i> +	Percentage	<i>P</i> value
Symptoms				
No	80	57	71.3%	0.02
Yes	29	14	48.3%	
Endoscopic findings ^a in patients without symptoms				
Erythema				<0.01
–	20	19	95.0%	
+, 2+, 3+	60	38	63.3%	
Edema				NS
–	29	24	82.8%	
+, 2+, 3+	51	33	64.7%	
Bile reflux				0.03
–	46	37	80.4%	
+, 2+	34	20	58.8%	

^a Graded according to the Sydney system [22] and reference [2]

and heartburn. There was a significantly lower prevalence of *H. pylori* infection in patients with symptoms than in those without symptoms (Table 3). As for endoscopic findings, erythema, edema, and bile reflux were noted in 71.3%, 60.9%, 43.5% respectively, of the 109 patients. These endoscopic findings indicated stomal gastritis in the GR. Inverse correlations were found between *H. pylori* positivity and the grades of erythema, edema, and bile reflux (Fig. 2). Moreover, a high prevalence of *H. pylori* infection was very frequently found in asymptomatic patients without these endoscopic findings (Table 3). Endoscopically, atrophic mucosa was found to have spread only in the lesser curvature of the GR (+), in more than one-half of the GR (2+), and in more than two-thirds (3+) of the GR [22] in 39 (33.9%), 30 (26.1%), and 8 (7.0%), of the patients, respectively. In patients with severe mucosal atrophy (3+), significantly lower *H. pylori* prevalence was shown than in patients with milder spread of atrophic mucosa.

Histologically, irregular glandular dilatation in the anastomosis area is as a typical finding in stomal gastritis. *H. pylori* positivity showed no correlation with glandular irregularity, and an inverse correlation with glandular dilatation (data not shown). Histologically,

Fig. 2. Correlation between endoscopic findings (graded according to the Sydney system [22] and references [2]) and *Helicobacter pylori* prevalence in the gastric remnant (GR). Inverse correlations were found between *Helicobacter pylori* positivity and the grades of erythema, edema, and bile reflux. In patients with severe mucosal atrophy (3+), significantly lower *Helicobacter pylori* prevalence was shown than in patients with mildly atrophic mucosa (* $P < 0.01$)

atrophic change in the mucosa was found in 34.9% of samples in the stomal area and in 34.9% of samples in the body, respectively. As shown in Fig. 3, *H. pylori* prevalence was highest in mildly atrophic mucosa and decreased along with the progression of atrophic change of the mucosa. Intestinal metaplasia was occasionally found in atrophic mucosa in the GR; 6.4% of atrophic mucosal samples from the stomal area and 15.6% from the body demonstrated intestinal metaplasia, to varying degrees. The existence of intestinal metaplasia was not correlated with *H. pylori* infection status. In patients with *H. pylori* infection, 95.8% (68/71) were positive for mononuclear cell infiltration, and 71.8% (51/71) were positive for polymorphonuclear neutrophil infiltration. In *H. pylori*-negative patients, on the other hand, 71.1% (27/38) and 34.2% (13/38), respectively, were positive for these histological findings. The grades of mononuclear cell infiltration and polymorphonuclear

Fig. 3. Correlation between histological findings (assessed according to the updated Sydney system [24] and *Helicobacter pylori* prevalence in the GR. Infiltrations of mononuclear cells, and polymorphonuclear neutrophils, suggesting chronic and acute gastritis, respectively were significantly correlated with *Helicobacter pylori* infection. *Helicobacter pylori* prevalence was highest in the mildly atrophic mucosa and decreased with the progression in atrophic change in the mucosa. Intestinal metaplasia was not correlated with *Helicobacter pylori* infection (* $P < 0.01$)

neutrophil infiltration were significantly correlated with *H. pylori* infection status (Fig. 3).

Discussion

In Japan, the estimated prevalence of *H. pylori* in primary gastric cancer patients was reported to be 70%–80%. Thus, our data for *H. pylori* prevalence, of approximately 65% overall, and the initial high prevalence of more than 75% were in line with these results. We observed that the prevalence decreased with time after surgery, although there was no intentional eradication. Inhibition of *H. pylori* colonization by bile reflux has been observed [16], and a transition from *H. pylori*-associated gastritis to reflux gastritis in the GR after peptic ulcer surgery was suggested [25]. Similar findings were demonstrated in the present study. The prevalence of *H. pylori* infection was significantly lower in patients with severe bile reflux than in patients without bile reflux. More rapid disappearance of *H. pylori* infection was found in patients with B-II reconstruction than in those with B-I. Billroth-II reconstruction is often associated with bile reflux. Bile reflux often causes stomal gastritis, which was characterized endoscopically by moderate to severe erythema and/or edema in the anastomosis portion. Each of these endoscopic findings was inversely associated with the prevalence of *H. pylori* infection in this study. These observations suggested

that *H. pylori* colonization is strongly inhibited, or naturally eradicated, by stomal gastritis caused by bile reflux. Thus, on the basis of these observation, spontaneous eradication may be expected in patients with severe stomal gastritis caused by bile reflux.

The prevalence of *H. pylori* infection was significantly lower in patients with wide-spread mucosal atrophy than in those with milder atrophic spread. Moreover, the prevalence was observed to increase, and then decrease along with the histological grade of mucosal atrophy. An atrophic mucosa is considered not to provide a sufficient environment for *H. pylori* colonization [26]. However, mucosa with widespread atrophy is considered the most risky mucosa for carcinogenesis, and is also considered to be the precursor of intestinal-type gastric carcinoma [12–14]. Thus, patients with mild atrophy with *H. pylori* infection may represent the most important targets for *H. pylori* eradication therapy.

The prevalence of *H. pylori* infection in Japan was considered to have increased with age, with a plateau of approximately 80% being reached in the fourth decade [27]. In our study, younger patients had a significantly higher prevalence of *H. pylori* infection in the GR than the older patients. The reason for the decrease in prevalence that we observed in the older population could reflect the spontaneous disappearance of *H. pylori* in patients in whom there was a long period after the operation. Interestingly, patients with a short follow-up period were also found among the older patients in the *H. pylori*-negative group. Fukuda et al. [28] suggested that *H. pylori* had already been eradicated in an older population with primary gastric cancer at the time of operation. Although we did not examine *H. pylori* prevalence before the operation, our data is in line with their observation. On the other hand, it has been suggested that there is a more intimate involvement of *H. pylori* infection in gastric cancer development in the younger population than in the older population [29]. Thus, our results indicate that younger patients with a GR may be better candidates for *H. pylori* eradication therapy than older patients.

Although *H. pylori*-related active gastritis was found in a considerable number of GRs after gastric cancer surgery, it was not associated with clinical symptoms in this study. Indeed a significant inverse correlation was shown between *H. pylori* prevalence and the clinical symptoms. Thus, *H. pylori* prevalence itself did not seem to cause the clinical symptoms. Furthermore, a surprisingly high prevalence of *H. pylori* was noted in patients with no symptoms and no endoscopic findings of erythema, edema, or bile reflux. Thus, we emphasized the importance of annual follow-up endoscopic examination after gastric cancer surgery to detect *H. pylori*-related gastritis in the GR, which progresses silently.

In this study, we demonstrated a typical pattern of *H. pylori* infection in the GR after gastric cancer surgery. Patients younger than 70 years of age, without bile reflux and with mild atrophic gastritis may have the highest probability of *H. pylori* colonization in the GR after gastric cancer surgery. The prevalence of *H. pylori* infection in such patients was estimated to be more than 90% from our results, and *H. pylori*-related gastritis was persistent in these patients. Although the spontaneous disappearance of *H. pylori* infection in the GR occurs in about two-thirds of patients this does not indicate that the risk of carcinogenesis is decreased, rather, that it is increased, as a consequence of either conversion to reflux gastritis or the presence of widespread atrophic gastritis. Further, prospective, studies enrolling a large number of patients with GRs, are needed to determine the effect of *H. pylori* eradication in the prevention of second primary cancer in the GR. Furthermore, as the environment of the GR is quite different from that of the normal stomach, suitable and reliable methods of effective *H. pylori* eradication should be studied for patients with a GR.

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