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Role of *Helicobacter pylori* in stomach cancer after partial gastrectomy for benign ulcer disease

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ABSTRACT

Objective: to determine the prevalence of *Helicobacter pylori* infection in patients having undergone gastrectomy for non-neoplastic disease who later developed gastric stump cancer.

Material and methods: retrospective study of all patients with partial gastrectomy for non-malignant peptic disease who were submitted to an endoscopic exploration between 1995 and 2001. A comparison was made of major clinical and histological characteristics, and the presence of *Helicobacter pylori* among patients with and without gastric cancer in the stomach remnant.

Results: a total of 73 patients were studied in this period. Fifteen patients (20.5%) had remnant-stump gastric cancer. All but one were adenocarcinomas (71% intestinal and 29% diffuse, respectively). The average time between diagnosis of gastric cancer and previous gastrectomy was 32 (14-48) years. There was a higher detection rate of *Helicobacter pylori* in patients with cancer in the gastric remnant (100 *vs.* 81.5%, respectively, $p < 0.07$). No relationship was seen between type of gastric reconstruction (Billroth I or II) and rate of *Helicobacter pylori* detection.

Conclusions: *Helicobacter pylori* infection is frequent in patients with previous gastrectomy for non-neoplastic disease. The results of the study suggest that *Helicobacter pylori* infection may play a role in gastric stump cancer.

Key words: Gastric stump cancer. *Helicobacter pylori.*

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INTRODUCTION

In 1994 the consensus group comprised of the World Health Organization and the International Agency for Research on Cancer stated that there was enough epidemiologic and histologic evidence to classify *H. pylori* as a definitive carcinogen (1). In that sense, a previous meta-analysis suggests that chronic *H. pylori* infection induces a two- to three-fold increase in the risk of gastric cancer (2-4), and a recent prospective study found that *H. pylori* is associated with the development of gastric cancer (5).

In patients submitted to partial gastrectomy for benign ulcer disease, an increased risk of gastric stump cancer after a long latency period has been noted (6,7), and a previous meta-analysis suggests that the risk is higher fifteen years after gastric surgery (8). In contrast to gastric cancer in the intact stomach, where *H. pylori* has a predominant role in carcinogenesis, bile reflux, an invariable consequence of operations that remove or by-pass the pylorus, is thought to be a major factor in carcinogenesis after gastric surgery (9). The role of *H. pylori* in gastric stump cancer has been the main topic in several studies, although such role is not absolutely clear yet. There are also studies where *H. pylori* and biliary reflux to the gastric stump obviously play a synergistic role in cell proliferation. It has been suggested that alkaline intragastric pH as induced by bile reflux produces an unfavorable microambient for *H. pylori* colonization (10,11). In that sense, it has been proved that bile salts seem to have a bactericidal effect on *H. pylori*, and following a Billroth resection *H. pylori* rapidly disappears from the gastric remnant (12). Moreover, the low incidence of *H. pylori* infection of the gastric stump detected in previous studies determines that the cellular proliferation rate resulting from bile acid reflux has been again implicated as the main factor involved in the pathogenesis of gastric stump cancer (13-15).

The aim of this retrospective study was to determine the prevalence of *H. pylori* infection in gastric stump cancer for patients surgically treated for benign peptic ulcer disease.

MATERIAL AND METHODS

Model design and patient selection

This study was performed retrospectively. Between January 1995 and December 2001, at the Endoscopy Unit of the Digestive Department, a gastroscopy was performed on 116 patients who had previously undergone partial gastrectomy for benign peptic ulcer. In 73 patients (63%), a sample for histological study was available in the files of Department of Pathology (samples obtained during endoscopy or surgical specimen). It is important to point out that carcinomas from the gastric cardia and patients with less than 10 years of follow-up were excluded. All gastric stump cancers were located near the gastro-enterostoma.

In order to establish the role of *H. pylori* infection in gastric cancer after previous partial gastrectomy we established two subgroups for the analysis: group 1 (patients with gastric stump cancer) and group 2 (patients without cancer). A comparison of the main clinical (gender, age, reason for gastrectomy, type of gastric reconstruction), and histological variables (gastritis, metaplasia, presence of *H. pylori* infection) was carried out (9).

Histological assessment and *H. pylori* identification

Biopsy specimens or samples from gastrectomy were placed in 10% formaline, routinely processed, and then stained with hematoxylin and eosin. A modified Giemsa and Masson Trichromic stain was used to detect *H. pylori* infection. The histological type of gastric cancer was determined using Lauren's classification, and was then assigned to one of three groups: intestinal, diffuse or mixed (16). The non-neoplastic mucosa was examined for chronic inflammation, glandular atrophy, and intestinal metaplasia according to Sydney's classification. Histological examination and *H. pylori* status were evaluated independently by two pathologists.

Statistical methods

Continuous variables were expressed as mean ± standard deviation. Qualitative variables were evaluated by means of the χ^2 test, applying Yates' correction as required. Continuous variables with parametric and non-parametric distribution were compared by means of Student's t test and Mann-Whitney U test, respectively.

RESULTS

The baseline characteristics of patients studied are depicted in table I. Overall, *H. pylori* was detected in the gastric remnant of 63 patients (86%). In fifteen patients (20.5%) a gastric stump cancer was diagnosed. *H. pylori* colonization was detected in all patients (100%) with gastric stump cancer. All but one were gastric adenocarcinomas (71 and 29%, intestinal and diffuse types, respectively). In one patient a gastric T lymphoma was diagnosed. Average time between diagnosis of gastric cancer and previous gastrectomy was 32 (14-48) years, without differences in the time to last endoscopic follow-up in the non-cancer group (Table I).

Table I. Baseline characteristics of patients included in the study

Age at gastrectomy	38.9 ± 13.6
Gender (male/female)	64/9
Alcohol consumption	50%
Smokers	75%
Etiology for gastrectomy	
Gastric ulcer	20%
Duodenal ulcer	24%
Indeterminate location	56%
Gastrectomy type	
Billroth I	27%
Billroth II	73%
H. pylori positive	86%
Gastric stump cancer	15 (20%)

Although smoking status was more prevalent in the cancer group (93 *vs.* 69%, $p < 0.05$), no differences were observed in age, gender, alcohol consumption, etiology for gastrectomy, and type of Billroth reconstruction between groups: patients with or without gastric cancer (Fig. 1, Table II). Atrophy and intestinal metaplasia were more fre-

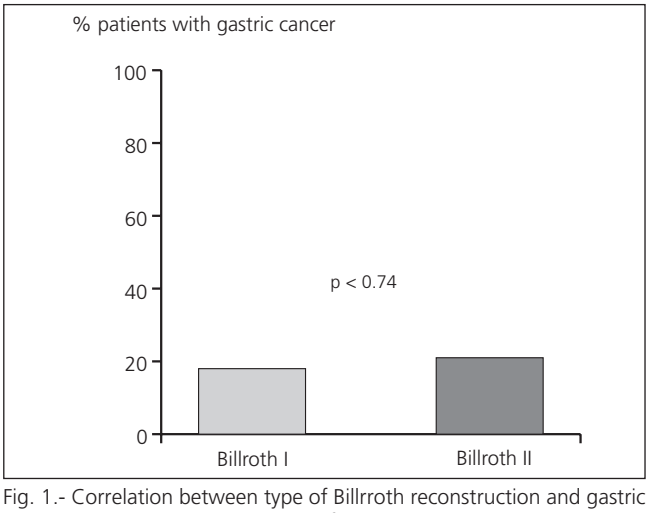

Fig. 1.- Correlation between type of Billrroth reconstruction and gastric cancer in patients surgically treated for non-malignant peptic disease. *Correlación entre el tipo de reconstrucción Billroth y el cáncer gástrico en pacientes operados por enfermedad péptica benigna.*

Table II. Comparative clinical data of patients with and without gastric stump cancer

	Gastric stump cancer (n = 15)	*No gastric stump cancer (n = 58)*	*p*
Age at gastrectomy	35 ± 12	39 ± 14	0.5
Time elapsed since gastrectomy	32 ± 11	29 ± 11	0.86
Gender (male/female)	13/2	49/5	0.47
Alcohol consumption	47%	52%	0.53
Smokers	93%	69%	0.05
Etiology for gastrectomy			
Gastric ulcer	14%	22%	
Duodenal ulcer	13%	26%	
Indeterminate location	73%	52%	0.34
Gastrectomy type			
Billroth I	20%	29%	
Billroth II	80%	71%	0.3
Histology of non-neoplastic mucosa			
Atrophy	29%	2%	
Metaplasia	57%	26%	
Displasia	0%	2%	
Chronic gastritis	14%	70%	0.03
H. pylori positive	100%	81.5%	0.07

quent in the non-neoplastic mucosa of patients with gastric stump cancer than in patients without cancer (29 and 57 *vs.* 2 and 26%, respectively). Although not reaching statistical significance, *H. pylori* detection was higher in patients with cancer in the gastric remnant (100 *vs.* 81,5%, respectively) ($p < 0.07$) (Fig. 2). No relationship was seen between type of gastric reconstruction (Billroth I or II) and rate of histologic *H. pylori* detection (Fig. 3).

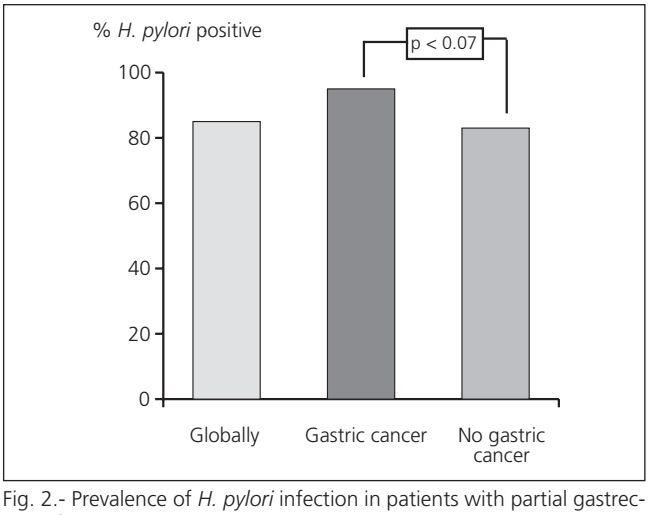

Fig. 2.- Prevalence of *H. pylori* infection in patients with partial gastrectomy for non-malignant peptic disease.
Prevalencia de la infección por H. pylori en pacientes con gastrectomía parcial por enfermedad ulcerosa benigna.

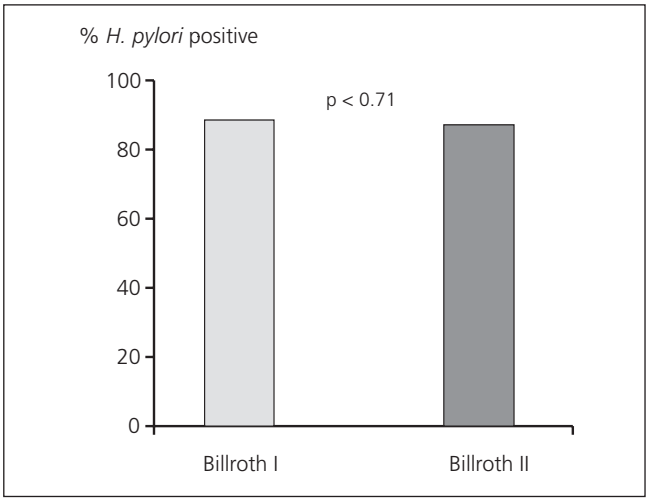

Fig. 3.- Correlation between type of Billroth reconstruction and *H. pylori* detection in patients surgically treated for non-malignant peptic disease.
Correlación entre el tipo de reconstrucción Billroth y la detección de la infección por Helicobacter pylori en pacientes tratados de enfermedad ulcerosa benigna.

DISCUSSION

After partial gastrectomy there is an increased risk of gastric cancer, and this risk increases steadily with the duration of the post-operative interval (6-8). Pathogenesis is not clear, but the increased proliferation of mucosal cells associated with chronic bile reflux seems to be a risk factor (17,18), and associations between bile reflux and intestinal metaplasia have been reported following gastric surgery (19). The currently dominant hypothesis is that intestinal metaplasia is a pre-cancerous condition occurring as a result of exposure to mutagens in hypochlorhydric gastric juice. Although in the intact stomach *H. pylori* infection has been considered a factor increasing the risk of gastric cancer (2-5), its role in the development of gastric stump cancer in patients surgically treated for benign ulcer disease is unclear.

Multiple studies have evaluated the prevalence of *H. pylori* in patients with gastric cancer (2-5). In few previous studies, the prevalence of *H. pylori* infection in patients with stump gastric cancer has been estimated at around 38% (14,20-24). Only one study (25), using polymerase chain reaction (PCR)-based methods to detect *H. pylori* DNA in the gastric juice, observed a higher prevalence (62.4%); however, this study included patients with partial gastrectomy for gastric cancer.

It has been advocated that the increase of bile acid reflux seen after a partial gastrectomy, more prevalent in patients with a Billroth II reconstruction, produces an unfavorable microenvironment for *H. pylori* infection and colonization, and could explain the low *H. pylori* detection in these patients. As previously indicated, it has been proved that bile salts seem to have a bactericidal effect on *H. pylori*, and after a Billroth resection *H. pylori* disappears rapidly from the gastro-enterostoma (12,27). Moreover, the low incidence of *H. pylori* infection in the gastric stump as detected in previous studies reveals that the

cellular proliferation rate resulting from bile acid reflux has been again implicated as the main factor involved in the pathogenesis of gastric stump cancer (13-15). Due to the retrospective nature of our study, it has not been possible to quantitate bile reflux in our patients, but as in all patients with operations that remove or by-pass the pylorus, our patients would have a high intragastric pH (9).

Our results, with a noteworthy high prevalence of *H. pylori* infection in the gastric remnant, argue against the deletereous effect of an intragastric alkaline microenvironment in *H. pylori* colonization. It may be reasonable to think that *H. pylori* infection was acquired before gastrectomy, and all patients were operated on for untractable or complicated ulcer disease. In addition, differences in *H. pylori* prevalence may be due to the fact that the size of fragments studied were much larger in the stump cancer group. So, as infection may be sparse and irregular, larger samples could allow a more detailed study, thus giving a higher chance of detecting patchy *H. pylori* infection.

As previously described (10,21,27), although not reaching statistical significance in our study, perhaps due to the low number of cases, patients with Billroth I reconstructions had a higher prevalence of *H. pylori* infection than those with Billroth II reconstructions. *H. pylori* colonization in the gastric stump has not been correlated with any one of the evaluated variables (age, gender, reason for gastrectomy, type of anastomosis or interval between surgery and *H. pylori* status).

In our study, chronic gastritis was detected in 70% of patients without gastric cancer. Although *H. pylori* infection has not been implied in ulcer relapse in gastrectomized patients for benign peptic disease (23), persistent infection produces residual gastritis in the gastric stump and epithelial cell proliferation in the corpus (20). One study suggests that *H. pylori* eradication induces a regression of gastritis in the remnant (28), and *H. pylori*-induced gastritis has a synergic effect with bile reflux in stimulating cellular proliferation in the gastric stump (20,21). Moreover, a study of cell proliferation in patients with previous gastrectomy has shown that those positive for *H. pylori* had higher levels of cell proliferation than those who tested negative for this organism (22), suggesting that both may be implicated in gastric carcinogenesis in these patients.

Although, in the present study, the differential prevalence of *H. pylori* infection between both groups (with and without gastric cancer) did not reach statistical significance, the high prevalence of *H. pylori* infection in patients with gastric cancer (100% of patients) deserves some attention. Probably, with a greater number of patients, differences would reach statistical significance. And secondly, the high prevalence of *H. pylori* infection in both groups and the high efficacy of various treatments (29) reinforce the need for *H. pylori* eradication in patients with partial gastrectomy for benign ulcer disease, not only for the ulcerous antecedent but also as a measure to prevent gastric cancer.

In conclusion, *H. pylori* colonization in patients undergoing partial gastrectomy for benign ulcer disease does not seem to be influenced by bile reflux, and the results of the present study suggest that *H. pylori* may have a role in gastric carcinogenesis in gastrectomized patients.

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