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Clinicopathologic Characteristics of *Helicobacter Pyloric* Seropositive Gastric Adenocarcinomas

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To compare and characterize retrospectively the clinicopathologic features of gastric cancers with and without previous *Helicobacter pylori* infection, we determined the preoperative seropositivity of *H. pylori* in 151 patients who had undergone gastric resection for primary gastric adenocarcinoma between 1988 and 1993. The overall seroprevalence of *H. pylori* was 60.9%. *H. pylori*-positive gastric cancers were frequently associated ($p < 0.05$) with macroscopic localized types (Borrmann I and II) in which negative cancer associated with infiltrative types (Borrmann III and IV) and cancer invasion of the duodenum. Multivariate analysis showed that *H. pylori* seropositivity was not an independent prognostic factor. Pathologic tumor-node-metastases (TNM) stage remained the only prognostic indicator. Our study suggests that *H. pylori* has a significant impact on the clinically relevant tumor biology of gastric cancer. Investigation along this line is warranted.
Key Words: *Helicobacter pylori* – Gastric cancer – Prognosis.

Environmental factors have long been postulated to play a role in the pathogenesis of chronic gastritis and gastric cancer (1,2). Since their first successful culture in 1982, *Helicobacter pylori* has attracted increasing attention because of its potential role in gastroduodenal diseases (3,4). Because this strain of bacteria is considered to be the primary cause of chronic antral gastritis, it may well play a role in gastric carcinogenesis, as has recently been suggested in many epidemiologic studies (5-10). Aside from the putative role in carcinogenesis, the specific cancer biology of *H. pylori*-associated gastric cancer also may be an important clinical problem. However, this issue has seldom been addressed. To investigate the clinicopathologic features and prognostic association between *H. pylori* and gastric cancer, we analyzed the status of *H. pylori* infection in 151 patients with resectable cancer to determine its clinical implication.

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MATERIALS AND METHODS

Subjects

One hundred fifty-one patients who had undergone gastric resection for primary gastric cancer at the National Taiwan University Hospital between 1988 and 1993 were included in this study. All of them had histologically verified adenocarcinoma in the stomach. The serum samples were supplied from the serum bank of the gastric cancer research center of this hospital. Fasting blood samples were obtained by venipuncture before surgery. After centrifugation, the serum was stored at −70°C until examination. All patients subsequently underwent gastrectomy. None of the patients received preoperative chemotherapy or radiotherapy. All patients were given regular follow-up examinations in the clinic, with a median period of follow-up of 3 years.

Serologic Detection of Immunoglobulin G Antibodies Against *H. pylori* in the Serum

Serum samples were tested for the presence of immunoglobulin G (IgG) antibodies against *H. pylori* using a highly sensitive and specific enzyme-linked immunosorbent assay (ELISA:HEL-p test, AMRAD, Australia). The antigen was an inactivated native antigen of *H. pylori*. The serum sample was diluted 1:200. The secondary antibody was a sheep antihuman IgG, conjugated horse peroxidase. A specimen was considered positive for IgG antibodies to *H. pylori* if its optical density (OD) value was greater than or equal to the upper cutoff value. The IgG assay had a sensitivity of 96% and a specificity of 93%. All assays were performed without knowledge of the clinicopathologic features of the subjects.

Clinicopathologic Study

The sex and age of the patient, the location of the tumor within the stomach, tumor size as measured in the surgical specimen, gross appearance (Borrmann type) (11), and type of surgical resection were obtained from medical records.

Surgeries were performed according to the guidelines of the Japanese Research Society for Gastric Cancer (12). Radical lymph node dissection R2/3 was routinely performed. When the tumor involved the proximal stomach, a total gastrectomy with splenectomy and subtotal pancreatectomy was performed. The operative mortality was 2.0%. A detailed review of the pathology record, including histopathologic examination of available tissue preparations, was performed to determine the depth of invasiveness within the gastric wall and the extent of metastases within regional lymph nodes. The stage was rated according to the TNM classification (13). In addition, the histology of gastric cancer was classified into diffuse and intestinal types according to Lauren's classification (14). DNA ploidy was examined by flow cytometry using fresh frozen tissue as described previously (15).

Statistical Analysis

Detailed clinicopathologic comparisons were made between *H. pylori*-positive and *H. pylori*-negative patients using the χ^2 test with Yates' correction and Student's *t* test. A p value of <0.05 was considered significant. Cumulative survival rates were calculated using the Kaplan–Meier method. The analysis was performed using the BMDP statistical package.

RESULTS

Seroprevalence of *H. pylori* Infection and Clinicopathologic Characteristics of Patients with Gastric Cancer

An overall seropositivity of *H. pylori* in patients with gastric cancer was 60.9% (92 of 151). The clinicopathologic results of the resected gastric cancer in both groups are summarized in Table 1. *H. pylori*-seropositive patients significantly associated with localized type (Borrmann I and II) gastric cancers and less duodenum involvement ($p < 0.05$).

TABLE 1. *Clinicopathologic data of 151 patients with resectable gastric adenocarcinoma*

Variable	No. of patients	*H. pylori* positive	*H. pylori* negative	p
Total number	151	92 (60.9)	59 (30.1)	
Mean age ± SD (yr)	58.8 ± 13.5	57.9 ± 12.7	60.3 ± 14.8	0.307
Sex (M/F)	84/67	56 (66.7)/36	31/28	0.106
Location				
Upper	30	18 (60.0)	12	0.095
Middle	33	15 (45.4)	18	
Lower	88	59 (67.0)	29	
Macroscopic type				
Early cancer	33	23 (69.7)	10	0.013[a]
Borrmann				
1/2 (localized)	26	21 (80.8)	5	
3/4 (infiltrated)	92	48 (52.3)	44	
Size (cm)				
<4	58	39 (67.2)	19	0.295
4–8	76	45 (59.2)	31	
>8	17	8 (47.0)	9	
Invasion depth				
t 1/2	61	41 (67.2)	20	0.192
t 3/4	90	51 (56.7)	39	
Lymph node metastases				
Negative	58	38 (65.5)	20	0.361
Positive N1/N2	93	54 (58.1)	39	
Distant metastases				
Negative	131	80 (61.1)	51	0.927
Positive	20	12 (60.0)	8	
Stage				
I	45	33 (73.3)	12	0.167
II	27	14 (51.8)	13	
III	46	28 (62.2)	18	
IV	34	17 (50.0)	16	
Histology				
Diffuse	91	53 (58.2)	38	0.450
Intestinal	60	39 (65.0)	21	
DNA ploidy				
Diploid	87	47 (54.0)	40	0.390
Aneuploid	43	27 (62.8)	16	
Duodenum invasion				
Negative	122	79 (64.8)	43	0.048[a]
Positive	29	13 (44.8)	16	
Section line involvement				
Negative	138	87 (63.0)	51	0.082
Positive	13	5 (38.5)	8	

Values in parentheses are percentages.
[a] Significant p value.

TABLE 2. *Operative and postoperative data*

	Total	*H. pylori* positive	*H. pylori* negative	p
Gastrectomy				
Total	44	24 (54.5)	20	0.303
Subtotal	107	68 (63.6)	39	
Operation morbidity	41 (27.2%)	22 (53.6)	19	0.291
Operation mortality	3 (2.0%)	2 (66.7)	1	
Postoperative chemotherapy				
Yes	63	43 (68.2)	20	0.079
No	88	49 (55.7)	39	
Recurrence				
Yes	55	32 (58.2)	23	0.601
No	96	60 (62.5)	36	

Values in parentheses are percentages.

Perioperative Data

There was no difference in the extent of gastric resection, operative morbidity, and mortality (Table 2). One operative death occurred in each group. Postoperative chemotherapy with 5-fluorouracil, adriamycin, and mitomycin was given to 63 patients. The percentage of patients with adjuvant chemotherapy did not differ significantly between the two groups (Table 2).

Recurrence and Survival

There was no difference in the survival curves of both groups after gastric cancer resection. Multivariate analysis using the Cox proportional hazards model showed that TNM staging was the only significant prognostic indicator (Table 3).

DISCUSSION

The overall seroprevalence of *Helicobacter pylori* in Taiwan has been reported to be 54.4% (16). This is considered to be intermediate as compared with the higher prevalence in India (98%) (17) and Africa (85%) (18) and the lower prevalence in the United Kingdom (30%) (19) and in the white population of the United States (37%) (20). Although ecological studies in Taiwan suggested an association between *H. pylori* infection and gastric cancer (21), 30–40% of the patients with gastric cancer in Taiwan have neither current nor previous infections with *H. pylori*. It was of interest to determine the different biological behaviors of gastric cancer with and without *H. pylori* infection.

TABLE 3. *Prognostic factors for survival after gastric cancer resection*

Variables	Hazard ratios	p
Sex	0.6514 (0.375–1.13)	0.1252
Age (1-year increase)	1.0135 (0.994–1.03)	0.1848
Location		
Upper	1.000	0.0287
Middle	0.602 (0.261–1.390)	
Lower	0.428 (0.226–0.809)	
Stage		
I	1.000	<0.0001[a]
II	12.370 (1.478–103.5	
III	26.350 (3.496–198.6)	
IV	67.881 (8.729–527.9)	
H. pylori	0.9062	0.7384

Values in parentheses are 95% confidence intervals.
[a] Significant p value.

Although a positive correlation between *H. pylori* infection and intestinal-type, noncardia cancer has been reported (8,9), these are not without contradiction (10,22). We found no difference of *H. pylori* infection as regards the location and histology type of patients with resectable gastric cancer. This observation supports the hypothesis of Sipponen et al. (23), which suggested that *H. pylori*–associated chronic gastritis provides the background for gastric cancer carcinogenesis, in which the intestinal type may be promoted by an atrophic stomach and the diffuse type by a nonatrophic gastritis mucosa. However, in our study, significant differences of seropositivity existed in gastric cancer patients with regard to gross type. *H. pylori*–positive gastric cancer tended to be of the localized gross type (Borrmann types I and II), and *H. pylori*–negative gastric cancer tended to be of the infiltrative gross type (Borrmann types III and IV). Therefore, *H. pylori*–negative gastric cancer had a higher ratio of duodenum invasion and section line involvement than *H. pylori*–positive gastric cancer. This finding implies a different biology of cancer growth in *H. pylori*–associated gastric cancer, which might influence the prognosis.

Survival rate after gastric cancer resection varies from 21% to >50% in different areas (24–28). Such differences have been attributed to the higher incidence of early cancer and the more aggressive surgical approach advocated by the Japanese. However, the therapeutic effect of extended lymph node dissection has so far not been demonstrated in randomized trials (29) and thus remains controversial. It is possible that a biologic difference does exist between different areas which may account for the difference of outcomes in different areas. In the United States, Fortner et al. has unexpectedly observed a significantly poorer survival rate in their

native-born patients than in foreign-born patients (30). Our study provides possible evidence that the biologic behavior of gastric cancers may vary with environmental factors involved in carcinogenesis. Although our data did not support *H. pylori* seropositivity as an independent prognostic indicator, this might be due to our small case numbers. *H. pylori* still might play a role in the prognosistic differences between areas of low and high seroprevalence rate. In addition, different surgical approaches in different areas may render valid comparison of therapeutic results more difficult (31). Further prospective, randomized clinical trials are indicated to clarify this issue.

Special attention should be addressed in surgical resection of *H. pylori*–associated gastric cancer. Adequate resection margins are important to ensure a cancer-free resection line and satisfactory local control of *H. pylori*–associated gastric cancer. Other biologic characteristics might also be associated with this specific type of gastric cancer. We have observed an attenuated response rate to chemotherapy for this specific type of gastric cancer (unpublished data), a phenomenon also observed in Epstein-Barr virus–associated lymphoma (32). Currently, we are studying the possible molecular mechanism involved in the development of drug resistance.

In summary, we have shown that (a) *H. pylori*–positive gastric cancer is significantly associated with the localized Borrman type and (b) *H. pylori*–negative gastric cancer has a higher rate of duodenum invasion, which was important for the surgical treatment of gastric cancer. Further investigations are needed to elucidate the inherent biologic characteristics and the clinical significance of this specific type of gastric cancer.

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