

The Effect of *Helicobacter Pylori* Eradication On Prognosis Of Postoperative Early Gastric Cancer: A Multicenter Study

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Abstract

Objective: To investigate the effect of *Helicobacter pylori* (*H. pylori*) eradication on the prognosis of postoperative early gastric cancer (EGC).

Methods: This is a retrospective study based on data from 6 hospitals. We identified patients with EGC who underwent curative gastrectomy from January 2010 to December 2016. All of the patients were tested for *H. pylori*. Patients were divided into two groups, the successful *H. pylori* eradication group (Group A) and the non-*H. pylori* eradication group (Group B), for calculating the disease-free survival (DFS) and overall survival (OS) of each group.

Result: Non-*H. pylori* eradication were statistically significant independent risk factors of overall survival (hazard ratio (HR), 1.760; 95% confidence interval (CI), 1.067-2.902; $P=0.027$) and disease-free survival (HR, 1.728; 95% CI, 1.077-2.772; $P=0.023$).

Conclusion: Eradication treatment for *H. pylori* can prevent the recurrence of postoperative early gastric cancer.

1. Introduction

Gastric cancer (GC) is the fifth most common cancer and the third deadly cancer, with more than 780000 annual deaths all over the world in 2018.¹ The highest incidence age-standardized rate is found in Eastern Asian populations, and the lowest in Northern Africa populations. The incidence of age-standardized rates in South Korea is 32.1 and 13.2 per 100000 individuals in men and women, respectively. *Helicobacter pylori* (*H. pylori*) plays a vital role in the occurrence and development of GC. Strong epidemiological and clinical evidence has shown that *H. pylori* infection is positively correlated with active chronic gastritis, peptic ulcers, atrophic gastritis, intestinal metaplasia, and gastric cancer.^{2,3} People who were infected with *H. pylori* have a more than 3-fold increase in risk of gastric cancer.⁴ The 5-year survival for gastric cancer in 2005–2009 was high (54–58%) in Japan and South Korea.⁵ And the five-year survival rate of early gastric cancer is more than 90%. A previous meta-analysis has suggested that *H. pylori* eradication reduced the risk of gastric cancer.⁶ However, the role of *H. pylori* eradication on the effect of prognosis on early gastric cancer has not been thoroughly examined. Recurrence is still a key factor affecting the survival of patients with EGC. This study aims to investigate the effect of *H. pylori* eradication on the postoperative prognosis of patients with EGC.

2. Methods

2.1. study population

We identified patients with EGC who underwent curative gastrectomy for gastric cancer from January 2010 to December 2016 in six hospitals (253 patients in Hunan Province Cancer Hospital, 109 patients in

the Second Xiangya Hospital of Central South University, 23 patients in the Second Affiliated Hospital of University of South China, 19 patients in the Central Hospital of Xiangtan City, 17 patients in Yongzhou Central Hospital and 8 patients in People Hospital of Qiyang county). All patients were tested for *H. pylori* by a carbon-14 (C-14) breath test. All cases were pathologically diagnosed as early gastric cancer and were consulted by the Multiple Disciplinary Team (MDT) in each center. Curative gastrectomy was performed on all patients who did not undergo or did not wish to undergo neoadjuvant chemotherapy. For a long time, there is no international consensus on whether patients with gastric cancer can benefit from *H. pylori* eradication treatment after surgery. Therefore, whether to treat with *H. pylori* eradication is mainly dependent on the patient's wishes. The exclusion criteria are as follows: negative *H. pylori*, *H. pylori* eradication failure. A total of 429 patients included were divided into two groups, the successful *H. pylori* eradication group (Group A) and the non-*H. pylori* eradication group (Group B). Group A received standard triple therapy (esomeprazole 20mg bis in die (bid), amoxicillin 1 g bid, and clarithromycin 0.5 g bid) orally for 7 days. *H. pylori* were identified by a C-14 breath test 1 month after treatment.

2.2. Definition

EGC is defined as gastric adenocarcinoma limited to the mucosa or submucosa, no matter whether it has lymph node metastasis or not. According to the Japanese Gastric Cancer Association principles,⁷ the stomach is anatomically divided into three portions, the lower (L) part, the middle (M) part, and the upper (U) part, the tumor size is measured by the maximum diameter of the tumor. The macroscopic classification of gastric cancer was divided into three types, elevated type (types 0-I, 0-II + Ia, 0-IIa, 0-IIa + Ib, 0-IIa + Ic), flat type (type 0-IIIb), and depressed type (types 0-IIIc, 0-III, 0-IIIc + Ia, and 0-III + Ia). According to WHO criteria, the histological classification of gastric cancer was classified into 2 different types, undifferentiated type (including mucinous adenocarcinoma, poorly differentiated tubular adenocarcinoma, and signet-ring cell carcinoma), and differentiated type (including well and moderately differentiated tubular adenocarcinoma and papillary adenocarcinoma).

2.3. Follow-up

Patients with EGC were followed up regularly after the radical gastrectomy. The last follow-up date was July 30, 2020. The patients were followed up every 6 months for the first 3 years after surgery, and then once a year until death or loss to follow-up. The follow-up information, including the time of patient relapse or death, were collected from hospital information systems, patients, or patients' family. Overall survival (OS) was calculated from the date of pathological diagnosis to death or the last date of follow-up. Disease-free survival (DFS) was calculated from the date of pathological diagnosis to recurrence or the last date of follow-up.

2.4. Statistics

The data were statistically processed using SPSS22.0 statistical software. Using Student t-test for comparing numerical data and the Pearson chi-square test for comparing categorical data. Data are shown as the mean \pm standard deviation. Univariate and multivariate analysis were performed by Cox proportional hazards regression model. The survival curve was traced using the Kaplan-Meier method, the

difference between curves was tested using the log-rank test. A 2-tailed *P* value less than 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristic

The baseline characteristics of the 429 patients are shown in Table 1. Group A and Group B have no significant differences in sex ratio, age, tumor size, the depth of invasion, histological classification, the macroscopic classification. The average age of patients was 56.01 ± 9.53 years. In total, the proportion of female patients (36.6%, 157/429) was lower than male patients (63.4%, 272/429) among patients with EGC. The size of the tumor was 24.5 ± 10.6 mm. The most common location was the lower third of the stomach (53.8%, 231/429), followed by the middle (32.6%, 140/429) and upper (13.5%, 58/429) parts of the stomach. The most common gross appearance was the depressed type (53.4%, 229/429), followed by the flat type (31.7%, 136/429), elevated type (14.9%, 64/429), and the proportion of differentiated type (49.2%, 211/429) and undifferentiated type (50.8%, 218/429) is close. In total, 210 (49.0%) patients had submucosal invasion and 41 patients (16.6%) had lymph node metastasis.

Table 1
Baseline characteristics of patients with EGC

	<i>Total</i>	<i>Group A</i>	<i>Group B</i>	<i>P-value</i>
Patient number	429	268	161	
Age (mean ± SD), y	55.94 ± 9.50	55.90 ± 9.49	56.01 ± 9.53	0.908
≥60	157(36.6%)	99(36.9%)	58(36.0%)	0.849
<60	272(63.4%)	169(63.1%)	103(64.0%)	
Gender				0.667
Male	272(63.4%)	172(64.2%)	100(62.1%)	
Female	157(36.6%)	96(35.8%)	61(38.9%)	
Tumor location				0.990
Upper	58(13.6%)	36 (13.4%)	22(13.7%)	
Middle	140(32.6%)	87 (32.5%)	53(32.9%)	
Lower	231(53.8%)	145(54.1%)	86(53.4%)	
Tumor size, mean ± SD, mm	24.5 ± 10.6	23.9 ± 10.5	25.3 ± 10.7	0.176
≥20	267(62.2%)	159(59.3%)	108(67.1%)	0.109
<20	162(37.8%)	109(40.7%)	53(32.9%)	
Depth of invasion				0.525
M	219(51.0%)	140(52.2%)	79(49.1%)	
SM	210(49.0%)	128(47.8%)	82(50.9%)	
Macroscopic type				0.510
Depressed	229(53.4%)	147(54.9%)	82(50.9%)	
Flat	136(31.7%)	85(31.7%)	51(31.7%)	
Elevate	64(14.9%)	36(13.4%)	28(17.4%)	
Node metastasis				0.924
Positive	71(16.6%)	44(16.4%)	27(16.8%)	
Negative	388(83.4%)	224(83.6%)	134(83.2%)	
Histology				0.404
Undifferentiated type	218(50.8%)	132(49.3%)	86(53.4%)	

	<i>Total</i>	<i>Group A</i>	<i>Group B</i>	<i>P-value</i>
Differentiated type	211(49.2%)	136(50.7%)	75(46.6%)	

3.2. Risk factors of recurrence among postoperative with early gastric cancer.

In univariate analysis, positive node metastasis (HR, 3.282; 95% CI, 2.008–5.363; $P < 0.001$), submucosal invasion (HR, 1.840; 95% CI, 1.151–2.940; $P = 0.011$), non-*H. pylori* eradication (HR, 1.638; 95% CI, 1.029–2.607; $P = 0.037$), undifferentiated type (HR, 2.898; 95% CI, 1.751–4.794; $P < 0.001$) were associated with recurrence among postoperative with early gastric cancer; In multivariate analysis, positive node metastasis (HR, 3.161; 95% CI, 1.860–5.371; $P < 0.001$), undifferentiated type (HR, 2.534; 95% CI, 1.503–4.272; $P < 0.001$), non-*H. pylori* eradication (HR, 1.728; 95% CI, 1.077–2.772; $P = 0.023$) were statistically significant independent risk factors of recurrence shown in Table 2.

Table 2
Predictive factors of recurrence of postoperative early gastric cancer

	Univariate			Multivariate		
	HR	95%CI	P value	HR	95%CI	P value
Age	1.412	0.882–2.261	0.151	1.304	0.800-2.127	0.287
Gender	0.894	0.554–1.444	0.648	1.196	0.727–1.968	0.481
Tumor location	0.840	0.617–1.144	0.269	1.030	0.740–1.434	0.860
Tumor size	0.971	0.610–1.544	0.900	0.953	0.589–1.541	0.845
Depth of invasion	1.840	1.151–2.940	0.011	2.235	1.378–3.625	0.001
Macroscopic type	0.874	0.628–1.217	0.426	0.816	0.581–1.148	0.243
Node metastasis	3.282	2.008–5.363	< 0.001	3.161	1.860–5.371	< 0.001
Histology	2.898	1.751–4.794	< 0.001	2.534	1.503–4.272	< 0.001
Hp eradication	1.638	1.029–2.607	0.037	1.728	1.077–2.772	0.023

3.3. Risk factors of overall survival among postoperative with early gastric cancer.

In univariate analysis, age > 60 (HR, 3.397; 95% CI, 2.079–5.551; $P < 0.001$), positive node metastasis (HR, 3.712; 95% CI, 2.252–6.117; $P < 0.001$), submucosal invasion (HR, 1.861; 95% CI, 1.140–3.037; $P = 0.013$), non-*H. pylori* eradication (HR, 1.622; 95% CI, 1.001–2.628; $P = 0.036$), undifferentiated type (HR, 3.059; 95% CI, 1.791–5.225; $P < 0.001$) were associated with overall survival among postoperative with early gastric cancer. In multivariate analysis, age > 60 (HR, 3.250; 95% CI, 1.957–5.396; $P < 0.001$), positive

node metastasis (HR, 3.669; 95% CI, 2.107–6.390; $P < 0.001$), undifferentiated type (HR, 2.074; 95% CI, 1.180–3.647; $P = 0.011$), non-*H. pylori* eradication (HR, 1.760; 95% CI, 1.067–2.902; $P = 0.027$) were statistically significant independent risk factors of overall survival shown in Table 3.

Table 3
Predictive factors of overall survival of postoperative early gastric cancer

	<i>Univariate</i>			<i>Multivariate</i>		
	HR	95%CI	P value	HR	95%CI	P value
Age	3.397	2.079–5.551	< 0.001	3.250	1.957–5.396	< 0.001
Gender	0.903	0.548–1.489	0.689	1.422	0.834–2.424	0.196
Tumor location	0.769	0.560–1.057	0.106	0.839	0.609–1.156	0.283
Tumor size	1.227	0.741–2.033	0.427	1.206	0.718–2.028	0.479
Depth of invasion	1.861	1.140–3.037	0.013	2.255	1.368–3.717	0.001
Macroscopic type	0.872	0.612–1.243	0.450	0.826	0.568–1.199	0.314
Node metastasis	3.712	2.252–6.117	< 0.001	3.669	2.107–6.390	< 0.001
Histology	3.059	1.791–5.225	< 0.001	2.074	1.180–3.647	0.011
Hp eradication	1.622	1.001–2.628	0.036	1.760	1.067–2.902	0.027

3.4. Prognosis and survival analysis.

67 patients (15.6%) died during a median follow-up of 69 months (range from 18 to 119 months). The 3-, 5-year survival rates were 98.5% and 93.6% in group A, and 96.9% and 86.6% in group B, respectively (Fig. 1A). It's obvious that the survival curve of group A was higher than that of group B, and the difference was statistically significant (log-rank $P = 0.034$). There were 73 patients (17.0%) with recurrence during the follow-up, and the 3-, 5-year recurrence rates were 1.2% and 9.3% in group A, and 2.6% and 16.4% in group B, respectively (Fig. 1B). It is shown that the recurrence rate was lower in group A than in group B (log-rank $P = 0.035$).

Discussion

The occurrence of gastric cancer is a long-term process involving multiple factors. The exact cause of gastric cancer is not fully understood. Since Warren and Mashall discovered *H. pylori* in 1983, the World Health Organization concluded in 1994 that *H. pylori* is a carcinogen and plays a causative role in the pathogenesis of gastric cancer.⁸ In the process of *H. pylori*-induced chronic inflammation and cancerization, multiple factors including bacterial factors, host factors, and environmental factors interact to form a complex network to respond to inflammation and promote damage repair. *H. pylori* eradication, used to treat functional dyspepsia and prevent peptic ulcer disease that relapses after early ulcers, was found to prevent gastric cancer in a meta-analysis, showing a 50% reduction in risk.^{9,10}

Hwang's research found that *H. pylori* eradication may prevent intestinal-type gastric cancer by regression of atrophic gastritis and intestinal metaplasia in a prospective study for up to 10 years.¹¹

Although the mechanism of *H. pylori* causing gastric cancer has been extensively studied, few studies have been conducted on whether *H. pylori* eradication after the occurrence of gastric cancer can prevent the recurrence of gastric cancer and its effect on the prognosis after radical gastrectomy. For a long time, there is no international consensus on whether patients with gastric cancer can benefit from *H. pylori* eradication treatment. Choi J found that eradication of *H. pylori* after endoscopic resection of gastric tumors did not significantly reduce the incidence of metachronous gastric carcinoma in a prospective trial.¹² While Il Ju Choi's research showed that patients with early gastric cancer who received *H. pylori* treatment had lower rates of metachronous gastric cancer and more improvement from baseline in the grade of gastric corpus atrophy than patients who received placebo¹³. Our conclusions are similar to theirs, eradication of *H. pylori* is also beneficial in preventing postoperative recurrence of gastric cancer.

In this study, *H. pylori* eradication resulted in a reduced risk of recurrence in patients with early gastric cancer after radical gastrectomy and a better prognosis than in those without eradication. This study provides evidence-based information on the prophylactic effect of *H. pylori* eradication on the postoperative recurrence of early gastric cancer, which may serve as a reference for determining whether or not to eradicate *H. pylori* in patients with gastric cancer after radical gastrectomy.

In conclusion, this retrospective study showed a decrease in the risk of postoperative recurrence of EGC after eradication treatment for *H. pylori*. Eradication treatment for *H. pylori* can prevent the recurrence of postoperative early gastric cancer.

Declarations

Availability of data and materials

Not applicable.

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Not applicable.

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Authors' contributions

CH and SL conceived and designed the experiments. LW, JF, SL, and FB carried out the study and analyzed the data. HL, HG, LZ, and TX collected data. XY, AQ and HB helped design the experiments. LW

wrote the paper. CH checked the paper. SL performed language correction. All authors read and approved the final manuscript.

Conflict of interest

The authors have no conflict of interest.

Consent for publication

Written informed consent for publication was obtained from all participants.

Ethics approval

This study was approved by the Ethics Committee of Hunan Cancer Hospital, the Second Xiangya Hospital of Central South University, the Second Affiliated Hospital of University of South China, the Central Hospital of Xiangtan City, Yongzhou Central Hospital, and People Hospital of Qiyang county. All patients involved in this study provided informed consent for the use of their personal data for research purposes. Informed consent was obtained from all individual participants included in the study.

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Figures

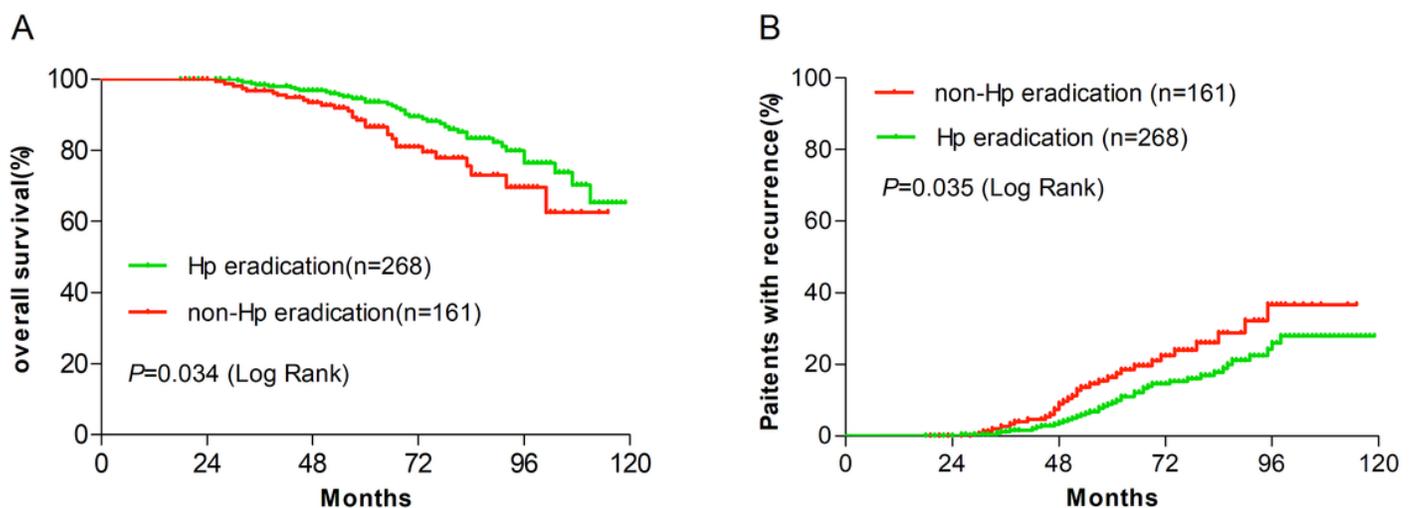


Figure 1

Kaplan–Meier Analysis of the rate of overall survival and recurrence. As shown in Figure 1, during a median follow-up of 69 months, 38 of 268 (14.2%) patients died in group A and 29 of 161 (18.0%)

patients died in group B (Figure 1A). There were 38 of 268 (15.3%) patients with recurrence in group A and 29 of 161 (19.9%) patients with recurrence in group B (Figure 1B).