Eradication of *Helicobacter pylori* for Primary Gastric Cancer and Secondary Gastric Cancer after EMR

Short running title: *H. pylori* Eradication and Gastric Cancer

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Abstract

Since almost gastric cancers develop from background of *H.pylori* infected gastric mucosa, *H. pylori* plays an important role in gastric carcinogenesis. Therefore, eradication of *H. pylori* has the possibility to prevent the incidence of gastric cancers. In the experimental studies, *H. pylori* eradication was proven to have the prophylaxis action of gastric cancers. However, the results of recent randomized controlled studies were absolutely controversial. In Japan, mucosal gastric cancer is usually resected by endoscopic treatment. As only a small part of the gastric mucosa is resected, secondary gastric cancer after endoscopic resection of primary gastric cancer often develops at another site of the stomach A non-randomized Japanese study involving 132 early gastric cancer patients reported that eradication of *H. pylori* after endoscopic resection tended to reduce the development of secondary gastric cancer. Also retrospective multi-center survey indicated that the incidence rate of secondary gastric cancer in the *H. pylori* eradicated group is about one third of that in the non-eradication group.

We conducted the large-scale multi-center randomized trial to confirm the effect of *H. pylori* eradication for secondary and residual gastric cancer after endoscopic resection. This study started from 2003 and is ongoing at present. Diagnosis of a new carcinoma at another site of the stomach is defined as primary endpoint, and recurrence of tumors at the resection site as a secondary endpoint. Five hundred forty-two subjects have been enrolled into the study. This study will have the statistical power to demonstrate whether *H. pylori* eradication decrease the incidence and recurrence of gastric cancer.

The relationship between H.pylori infection and gastric cancer

The relationship between *H.pylori* infection and gastric cancer has been evaluated in epidemiological studies, animal experiments, and clinical studies. In the epidemiological area, many studies using anti-*H. pylori* antibody were reported. Five meta-analysis studies of cohort studies, case-control studies, and nested case-control studies revealed a positive odds ratio between

H. pylori seropositivity and gastric cancer[1)-4)] (Table 1). In an animal model using Mongolian gerbil, *H. pylori* infection increased the incidence ratio of gastric cancer[5)-10)] (Table 2). Also gastric cancer prevention through *H .pylori* eradication based on this animal model has already been proved. Many factors are associated with the development of gastric cancer[11)- 13)] (Figure 1). Carcinogenesis factors include environments, host genetics, level of acid secretion, duration of *H. pylori* infection, and virulence of the *H. pylori* strains[14)]. Environmental factors futures consumption of high salt concentration, tobacco use, and so on. However, *H. pylori* play an important role in gastric carcinogenesis. *H. pylori* infection is necessary for carcinogenesis of gastric cancer, but not sufficient. Therefore, eradication of *H. pylori* has the possibility to prevent the incidence of gastric cancers. Outcome disease of *H. pylori* infection depends on the kind of gastritis[15)]. Intestinal type of gastric cancer used to occur from corpus predominant gastritis, while diffuse type of gastric cancer arose from pangastritis. Usually gastric cancer does not occur from antrum predominant gastritis that is background gastritis of duodenal ulcer.

However, compared to epidemiological studies and animal studies, there is not enough evidence from human intervention studies that was conducted to determine whether *H. pylori* eradication reduces the incidence of gastric cancer. The two results of recent large-scale randomized controlled studies in China were absolutely controversial[16)17)] (Table 3). Wong study showed that incidence rates were similar between participants receiving *H. pylori* eradication and those receiving placebo. On the other hand, Zhou study showed that *H. pylori* eradication significantly decreased the incidence of gastric cancer. The effect of *H. pylori* eradication in the prevention of primary gastric cancer has not to be confirmed in clinical interventional studies. A non-randomized Japanese study, so-called Uemura study, involving 132 early gastric cancer patients reported that eradication of *H. pylori* after endoscopic resection tended to reduce the development of secondary gastric cancer[18)]. Although the relationship between *H. pylori* infection and gastric cancer is now accepted, the effectiveness of *H. pylori* eradication for prevention of gastric cancer has not been clarified.

Retrospective study in Japan

It is not unusual for gastric cancers to be detected after successful eradication of *H. pylori*. However, the frequency of gastric cancer that occurred after successful eradication has not been investigated nationwidely. Two retrospective multi-center studies were conducted at 41 institutions in Japan for aim to investigate the incidence in Japan of primary and secondary gastric cancer after *H.pylori* eradication[19)20)]. The first study compared the incidence of primary gastric cancer in two groups that were followed for five years; H. pylori was successfully eradicated in the eradication group, but persisted in the non-eradication group. The second study compared the secondary gastric cancer of these groups whose primary cancer was removed by endoscopic treatment. Next, the characteristics of primary and secondary gastric cancer after successful eradication were compared.

3021 patients participated in the primary gastric cancer study. The follow-up period was significantly shorter in the eradication group. The Female-to-male ratio and duodenal ulcer ratio were significantly higher in the eradication group. Gastric cancers developed in 23 patients (1.3%) whose *H. pylori* was successfully eradicated compared to 44 patients (3.6%) with persistent *H. pylori* infection during the 7.7 year follow-up in the primary gastric cancer study. The incidence ratio of primary gastric cancer was significantly lower in the eradication group (Odds ratio=0.36; 95% Confidential interval=0.22-0.62).

2835 patients participated in the secondary gastric cancer study. Secondary gastric cancers developed in 8 patients (2.2%) whose *H. pylori* were successfully eradicated compared to 129 patients (5.2%) with persistent *H. pylori* infection. The incidence ratio of secondary gastric cancer was significantly lower in the eradication group (OR=0.42; 95%CI=0.20-0.86).

The characteristics of gastric cancer were investigated among three groups: primary gastric cancer in the non-eradication group as control; primary gastric cancer in the eradication group, and secondary gastric cancer in the eradication group. There were significant differences in tumor size

between control primary gastric cancer and secondary gastric cancer in the eradication group (Figure 2). The comparison of characteristics in gastric cancer revealed the rise of ulcer negative ratio, mucosal cancer ratio, intestinal type ratio in order of control, primary gastric cancer in eradication group, and secondary gastric cancer in eradication group. There was no difference in morphological type cancers among three groups (Figure 3). The retrospective study showed the possibility that *H.pylori* eradication reduced the development of gastric cancer. The characteristics of gastric cancer were retrospectively a little different between eradication and non-eradication groups.

Prospective study in Japan

In Japan, mucosal gastric cancer is usually resected by endoscopic treatment. Conventional endoscopic mucosal resection, so-called EMR, consists of three steps in principle. These are marking, lifting by submucosal injection, and snaring and cutting. There are different snaring methods such as EMR-Cup, EMR-2 channels, EMR-Ligation. According to gastric cancer treatment guidelines by the Japanese Gastric Cancer Association, conventional EMR should be indicated for mucosal cancer of intestinal type without evidence of ulcer or ulcer scar measuring less than 2cm in diameter[21)]. The recently developed EMR procedure, endoscopic submucosal dissection (ESD), makes *en bloc* resection possible for mucosal cancers greater than 2cm in diameter[22)]. The concept and technique of ESD is markedly different from conventional EMR. ESD removes tumor lesions using round cut and submucosal dissection without use of snare device[23)]. Therefore, the indication of endoscopic resection was expanded in the case of ESD. For example, all intestinal type mucosal cancers without ulceration indicate ESD regardless of cancer size. The number of endoscopic treatment for gastric cancer is increasing gradually in future.

As only a small part of the gastric mucosa is resected, secondary gastric cancer after endoscopic resection of primary gastric cancer often develops at another site of the stomach. The frequency

of secondary gastric cancer was reported 3 to 7 % (Table 4). We conducted the large-scale multi-center randomized trial to confirm the effect of *H. pylori* eradication for secondary and residual gastric cancer after endoscopic resection[24]. This study started from 2003 and is ongoing at present. Eligible subjects are *H. pylori* infected patients who are newly resected by endoscopic treatment as an early gastric cancer or who are in the post-resection follow up phase. Patients are being randomly allocated to the eradication or the control arms. Patients will be evaluated by endocscopy at 0.5, 1, 2, 3 years after randomization. Diagnosis of a new carcinoma at another site of the stomach is defined as primary endpoint, and recurrence of tumors at the resection site as a secondary endpoint. Comparison between eradication group and control (non-eradication) group is investigated using intention-to-treat analysis, per-protocol analysis, and time to recurrence analysis. Significant level is defined as p=0.01 in interim analyses, p=0.045 in final analyses. Five hundred forty-two subjects have been enrolled into the study from April 2001 to July 2003 and are being followed-up (Table 5). Interim analysis was performed on March 2005 when observed person-years exceeded 750. The p-value for the treatment difference on the primary endpoint did not satisfy the criteria for statistical significance. This study is still ongoing until the observation periods of all currently enrolled subjects exceed 3 years.

H. pylori infection has the possibility to both initiates and promotes the development of gastric cancer. On this hypothesis, eradication should both inhibit the occurrence of new gastric cancer as well as reduce the growth rate of those cancers that do occur (Figure 4). Because 3-years follow-up periods after successful eradication in this study is too short to evaluate whether eradication prevents new occurrence, this study probably evaluates clinical cancers developed from occult cancer, which existed but not detectable at the time of endoscopic treatment. If detective time of residual cancer in eradication group is delayed comparing with that in control group, the promoter effect of *H. pylori* infection is able to be proved. In another wards, *H. pylori* eradication may decrease the speed of gastric cancer growth.

Conclusion

In Conclusion, the retrospective study showed the possibility that *H.pylori* eradication reduced the incidence of gastric cancer. The randomized prospective study is still ongoing. Final analysis is planned on September this year

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Figure Legend

Figure 1. Although gastric cancer occure from *H. pylori* infected gastritis, many factors are associated with the development of gastric cancer.

Figure 2. The tumor size of gastric cancers were investigated among three groups. There were significant differences between control primary gastric cancer and secondary gastric cancer in the eradication group

Figure 3: The comparison of characteristics in gastric cancer revealed the rise of ulcer negative ratio, mucosal cancer ratio, intestinal type ratio in order of control, primary gastric cancer in eradication group, and secondary gastric cancer in eradication group.

Figure 4: *H. pylori* infection both initiates and promotes the development of gastric cancer. On this basis, eradication should both inhibit the occurrence of new gastric cancer as well as reduce the growth rate of those cancers that do occur

Table 1

Meta-analysis of the relationship between *H. pylori* seropositivity and gastric cancer

	Selected paper	Odds rate	95%CI
Huang	19 cohort,CC	1.92	1.32-2.78
Danesh	10 nested CC	2.5	1.9-3.4
Eslick	34 cohort,CC	2.04	1.69-2.45
Xue	21 CC	3.00	2.42-3.72

CC: case-control study

Table 2

Gastric carcinogenesis in *H.pylori*-infected Mongolian Gerbils

	strains	Chemical agents	Ca incidence	Histology	period
Watanabe (1998)	TN2GF4	None	10/27 (37%)	well	62 weeks
Honda (1999)	ATCC43504	None	2/5 (40%)	well	72 weeks
Hirayama (1999)	ATCC43504	None	1/56 (2%)	well	52 weeks
Sugiyama (1998)	ATCC43504	MNU	13/37 (35%)	5 well, 2 por 6 sig	40 weeks
Shimizu (1999)	ATCC43504	MNNG	15/25 (60%)	9 well, 1 por 4 sig	50 weeks
Tokieda (1999)	ATCC43504	MNNG	4/6 (67%)	well	52 weeks

Figure 1

Factors contributing to gastric carcinogenesis

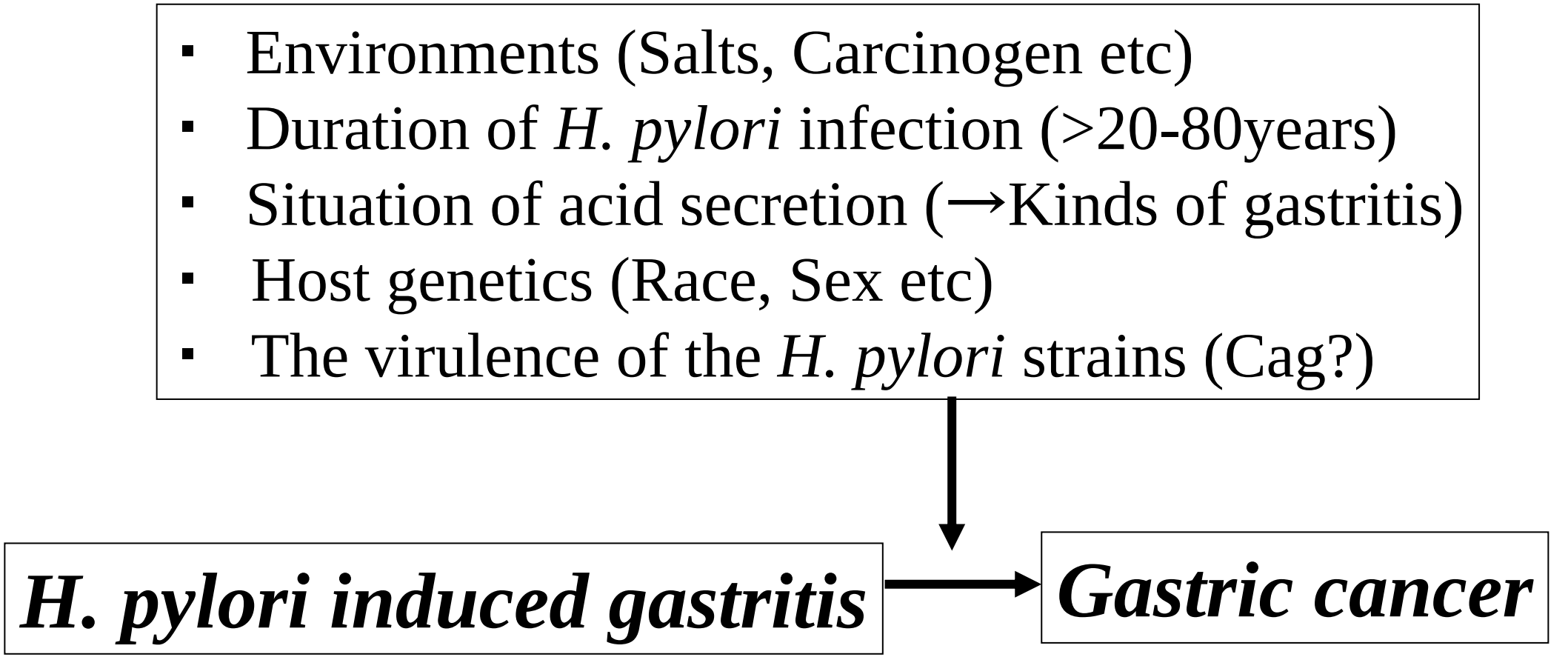

Table 3 **Interventional clinical study**

Wong BCY, JAMA:291,2004 Zhou L, Chin J Dig Dis:6,2005

Randomized placebo-controlled study in China

Follow-up 7.5 year

	Eradicated	Placebo
n	813	817
G.Ca	7	11
rates	0.86%	1.35%
	ns	

Follow-up 8 year

	Eradicated	Placebo
n	246	306
G.Ca	1	6
rates	0.41%	1.96%
	$p<0.05$	

Figure 2 **Size of gastric cancer in each groups**

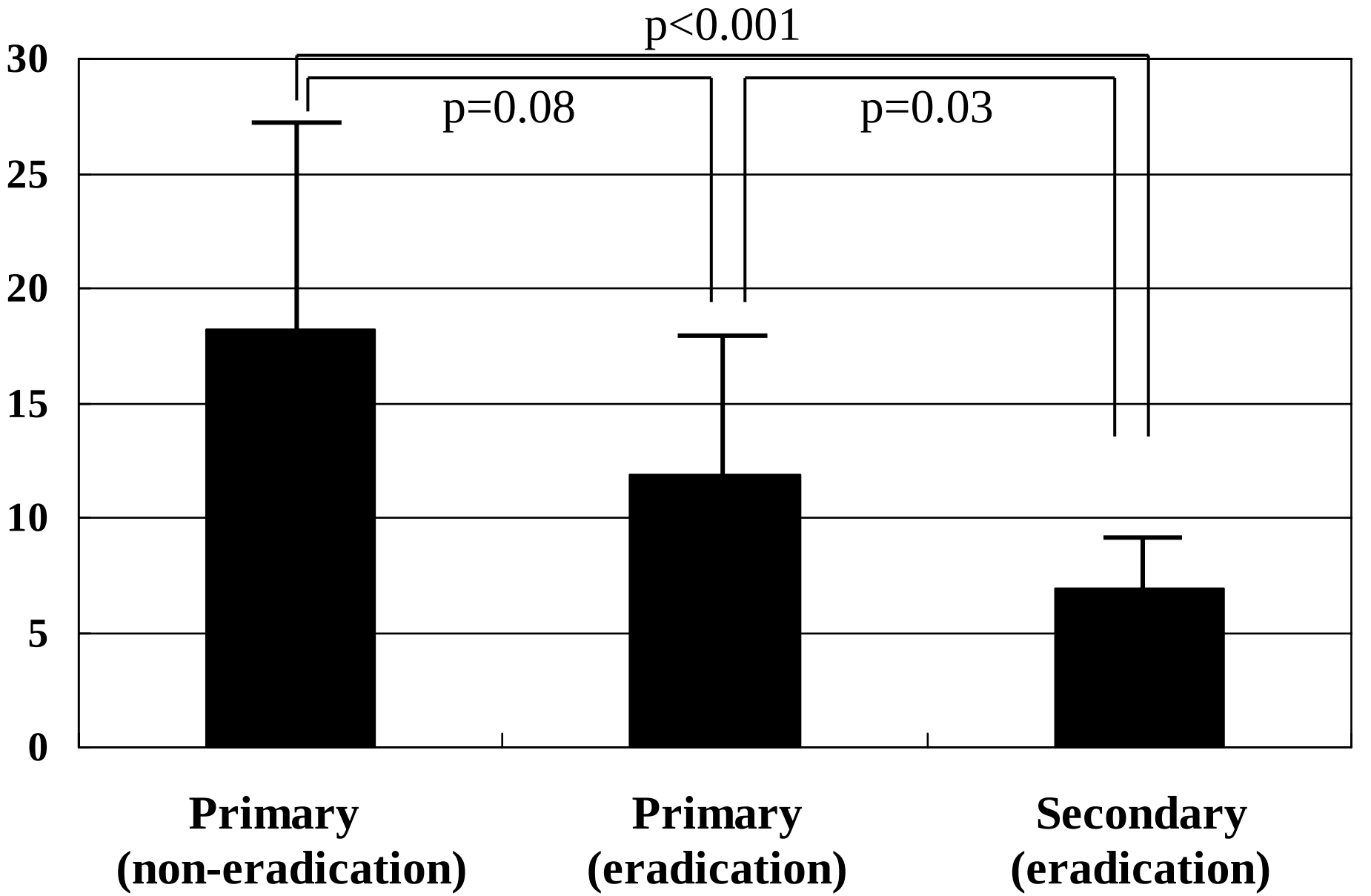

Figure 3

Characteristics of gastric cancer in each group

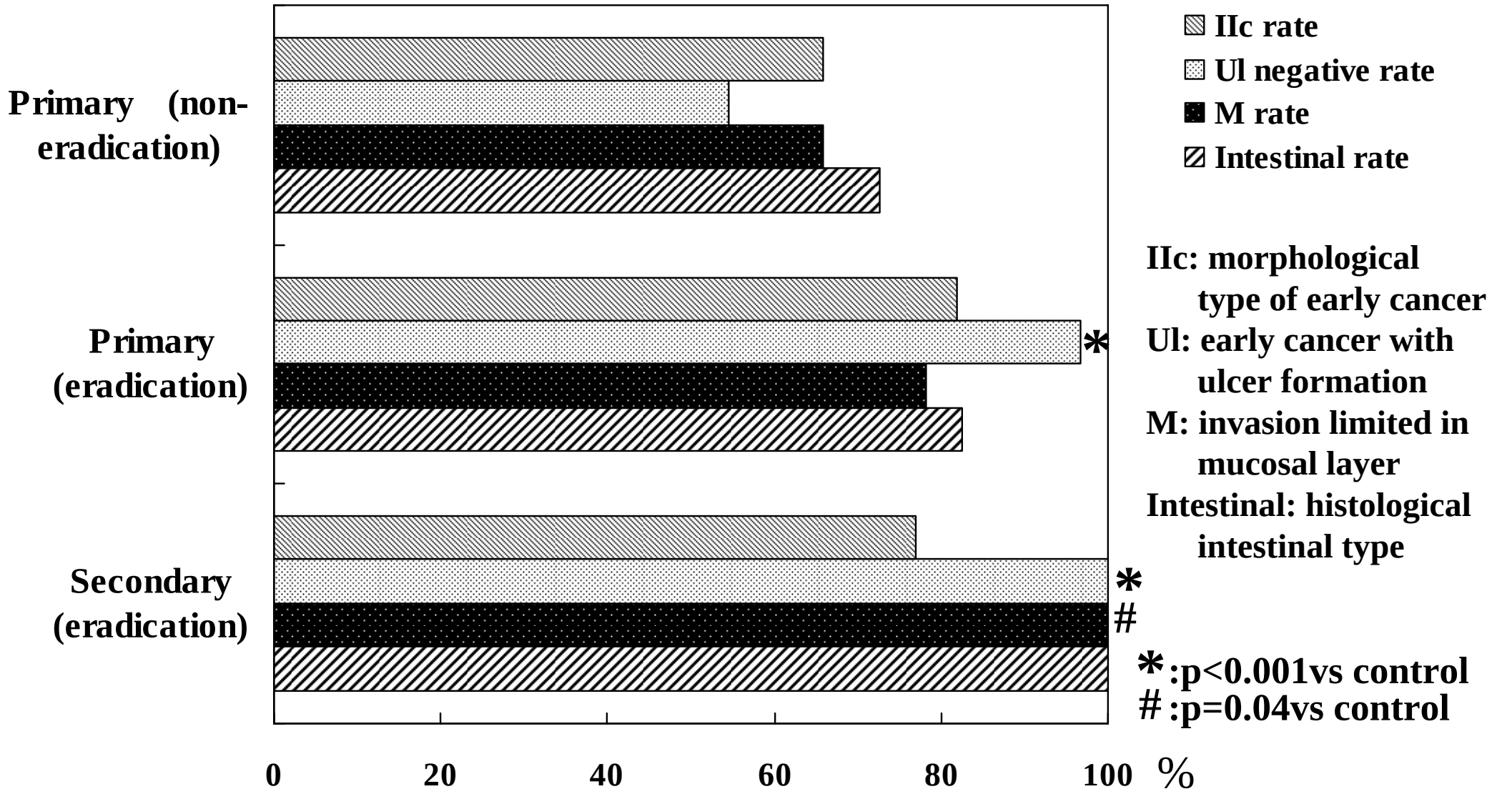

Table 4

The incidence rates of second gastric cancer after endoscopic resection of primary gastric early cancer

		Rates	Follow-up
Tada et al	1993	2.5%	Unknown
Tomimatsu et al	1994	5.6%	38.5 months
Mitsunaga et al	1998	6.3%	9months
Yoshikifu et al	1999	2.7%	30months
Yokoi et al	2005	6.8%	35months
Hosokawa et al	2005	7.4%	25months
Uedo et al	2005	3.8%	60months

Table 5 **Background of enrolled cases**

	Non-eradication	Eradication
Number	270	269
Age	68.1±8.2	67.2±8.6
M:F	2.9:1	2.8:1
Follow-up (year)	0.96	0.92
Complete resection /incomplete resection	4.1:1	6.4:1

Entry: April 2001 ~ July 2003

Figure 4

Hypothesis of *H. pylori* eradication effect