Prevention of Gastric Cancer by *Helicobacter pylori* Eradication

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Abstract

Attention was focused on whether the incidence of gastric cancer could be decreased by eradication of *Helicobacter pylori* (*H. pylori*) infection after *H. pylori* infection was found to be an important risk factor for gastric cancer. The Japan Gast Study Group (JGSG) planned a randomized study, with the primary endpoint being the development of gastric cancer after *H. pylori* eradication. To design a study with a fairly small sample size and short follow-up period, the conclusion was reached that the study should be conducted in patients who had undergone endoscopic mucosal resection (EMR) for early gastric cancer because they have the highest incidence of recurrent gastric cancer. There were no differences of age, gender, tumor site, histology, tumor depth, and tumor size between the two groups. The incidence of metachronous gastric cancer in eradication group was significantly lower than in control group in the analysis ignoring observation period (Odds ratio: 0.353, 95% CI: 0.161-0.775, $p=0.009$). Kaplan-Meier analysis revealed that the cumulative incidence of gastric cancer was different between the two groups. The Japanese Society for Helicobacter Research has published a guideline recommending that *H. pylori* infection should be treated by eradication therapy following this study. New evidence obtained from our study in Japan may be helpful for the prevention and eventually elimination of gastric cancer worldwide.

Key words: *Helicobacter pylori*, prevention of gastric cancer, eradication

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Helicobacter pylori (*H. pylori*) infects the gastric mucosa and causes pathological gastritis. *H. pylori* infection often persists for life and chronic inflammation of the gastric mucosa leads to a wide variety of upper gastrointestinal tract diseases, such as atrophic gastritis, gastric/duodenal ulcer, gastric cancer, gastric MALT lymphoma, and hyperplastic gastric polyps (1).

Irrespective of their histology, most gastric cancers arise from mucosa infected by *H. pylori*, and these tumors very rarely arise from gastric mucosa without inflammation. Therefore, *H. pylori* is considered to be the factor most strongly related to the development of gastric cancer. In Japan, 80% or more of *H. pylori*-infected persons will develop atrophic gastritis (2). Studies have shown that the presence of gastric mucosal atrophy and intestinal metaplasia increase the risk of gastric cancer (3). In 1994, the International Agency for Research on Cancer (IARC), a subsidiary of the

World Health Organization (WHO), designated *H. pylori* as a definite carcinogen for gastric cancer based on epidemiological data (4). After this, studies using Mongolian gerbils with *H. pylori* infection (5, 6) and a prospective study (7) conducted in Japan have clarified the association between *H. pylori* infection and gastric cancer. It has been an interesting issue for cancer researchers around the world as to whether or not eradication of *H. pylori* can prevent gastric cancer. In 2008, it was reported from Japan that the incidence of gastric cancer was decreased to approximately one-third by eradication of *H. pylori*, and this attracted attention internationally (8).

Preventing Gastric Cancer by *H. pylori* Eradication

After *H. pylori* infection was found to be an important

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risk factor for gastric cancer, attention was focused on whether the incidence of gastric cancer could be decreased by eradication of this infection. Intervention studies on the prevention of gastric cancer by *H. pylori* eradication in healthy subjects were conducted around the world.

In 2004, the results of a large-scale intervention study on gastric cancer in China were reported by Wong et al (9). They studied 1,630 people with *H. pylori* infection from the population of Fujian Province, where the mortality rate due to gastric cancer is high. The subjects were randomly assigned to an *H. pylori* eradication therapy group (n=817) or a placebo group (n=813), and were followed for 7.5 years from 1994 to 2002. All subjects were assessed by endoscopy at enrollment, after 5 years, and as needed. During follow-up, development of gastric cancer was observed in 7 subjects from the *H. pylori* eradication therapy group and in 11 subjects from the placebo group, with no significant difference between the 2 groups ($p=0.33$). For the subgroup without precancerous lesions (atrophy, intestinal metaplasia, and dysplasia), however, the incidence of gastric cancer was significantly lower in the *H. pylori* eradication therapy group than in the placebo group (0 vs. 6, $p=0.02$). All of the gastric cancers diagnosed after *H. pylori* eradication were advanced tumors and none of the subjects had early cancer. This seems bizarre to us because 60% of gastric cancers are early stage tumors in Japan (10).

During follow-up after endoscopic resection of gastric cancer, asynchronous multiple cancers (secondary cancers) are often found at sites other than the resection site. The length of follow-up has varied in reports to date, but the secondary cancer rate has ranged from 2.5 to 14% (11). Since endoscopic resection preserves the stomach different from gastric resection, it retains abnormal mucosa with atrophic gastritis or intestinal metaplasia caused by *H. pylori* infection, which represents field carcinogenesis, and the gastric environment is likely to promote the occurrence of secondary cancer. This is similar to the known association between liver cirrhosis and hepatocellular carcinoma. Therefore, if a treatment can reduce the incidence of metachronous gastric cancer under these circumstances, it seems likely to prevent gastric cancer. Uemura et al assigned patients who had undergone endoscopic therapy for early gastric cancer to an *H. pylori* eradication group or a non-eradication group and performed long-term follow-up. During approximately 5 years of follow-up, secondary gastric cancer was detected in 10 out of 67 patients from the non-eradication group (15%) versus none of 65 patients from the eradication group (12). Though the study was pioneering, it was not highly evaluated because the sample size was small and the patients were not strictly randomized.

The Japan Gast Study Group (JGSG) planned a randomized study, with the primary endpoint being the development of gastric cancer after *H. pylori* eradication. To design a study with a fairly small sample size and short follow-up period, the conclusion was reached that the study should be conducted in patients who had undergone endoscopic mu-

cosal resection (EMR) for early gastric cancer because they have the highest incidence of recurrent gastric cancer. Fifty-one institutions across Japan participated, and 544 patients who had undergone endoscopic resection for early gastric cancer were randomly assigned to an *H. pylori* eradication group or a non-eradication group. Then they were followed up with annual endoscopy to detect any recurrence of gastric cancer over 3 years. Enrollment started in January 2001 and ended in July 2003. There were no differences in patient characteristics or the histology of the primary tumors between the *H. pylori* eradication group and the control group. In both groups, intestinal metaplasia was observed in the gastric antrum of approximately 65% of patients and was seen at the body in approximately 45%. Gastric mucosal atrophy was moderate or severe in approximately 80%, and the range of atrophy was C3 or more in approximately 90%. During 3 years of follow-up, secondary cancers were observed in 9 patients from the *H. pylori* eradication group versus 24 patients from the control group, and there was a significant difference between the two groups (hazard ratio=0.339; 95% IC=0.157-0.729; $p=0.003$). There were no differences in age, gender, tumor site, histology, tumor depth, and tumor size between the two groups. However, a difference in the cumulative incidence rate was observed between the groups, with the risk ratio still being calculated after 3 years of follow-up. On the other hand, there was no significant difference of recurrence due to incomplete resection of the cancer in the eradication group (n=8) and the control group (n=10). Therefore, we conclude that eradication of *H. pylori* clearly suppresses the development of secondary cancer. This was the first randomized study in which patients who received intervention by *H. pylori* eradication therapy were compared with control patients and a significant difference was found in the primary endpoint (development of gastric cancer).

With respect to the effect of *H. pylori* eradication therapy on the prevention of gastric cancer, the data of Wong et al (9) seems to support the finding that eradication slows the progression of gastric cancer. However, it is possible that many of the patients in their study who were diagnosed as having no cancer might have actually had early gastric cancer. All of the cancers diagnosed during follow-up were advanced tumors, but taking into consideration the diagnostic techniques used in Japan, it is hard to believe that no early gastric cancers were detected in their study. Therefore, it seems their diagnostic sensitivity to detect early gastric cancer might have not been sufficient. In their study, the progression of early cancer to advanced cancer was slowed in the *H. pylori* eradication group, probably due to the effect of eradication therapy. In our study, however, even if we failed to detect early gastric cancer at other sites during EMR, the probability might be as low as only a few percent. Unlike the study of Wong et al with probable failure to detect early cancer, our results strongly suggested a suppressive effect of *H. pylori* eradication on gastric cancer (Fig. 1). When considering the suppressive effect of *H. pylori* eradication, in

Figure 1. Difference in the effect of eradication of *H. pylori* to prevent gastric cancer between two studies.

Figure. 2 Effect of eradication of *H. pylori* in the development of gastric cancer.

patients with early cancer that was missed during the initial endoscopic resection procedure eradication therapy may slow tumor growth, but recurrence will eventually occur at a site different from the resection site. The potential effect of *H. pylori* eradication on latent cancer (defined as tiny cancers due to chronic *H. pylori* infection that cannot be detected by endoscopy) is to slow its growth, to almost completely suppress it (zero growth), or to suppress it completely (negative growth). It would be expected that recurrence after *H. pylori* eradication often occurs in patients with undetected early cancer and patients with slowly growing latent cancer (Fig. 2). Based on the results of the JGSG study, *H. pylori* eradication may also be effective in patients who have early gastric cancer with mucosal atrophy and intestinal metaplasia.

The Japanese Society for Helicobacter Research has published a guideline recommending that *H. pylori* infection should be treated by eradication therapy (13). Although some studies have pointed out that there are theoretically some other outcomes following eradication therapy (e.g. development of GERD and an increased incidence of allergic disease) none has been proven, it was concluded that the advantages overwhelmingly outweigh the disadvantages in Ja-

pan where 50,000 people die from gastric cancer annually. As noted above, the WHO has concluded that *H. pylori* is the major cause of gastric cancer. We showed that gastric atrophy is the precursor lesion. It follows that eradication of *H. pylori* before atrophy develops will completely prevent gastric cancer. Eradication after development of atrophy will markedly reduce cancer development. It is problematic that the therapy recommended in the guideline cannot be performed under the Japanese national health insurance system due to limitations of the system. However, the Society has the responsibility to include the most advanced standard therapy in the guideline. It is difficult to explain how to apply the guideline in routine medical practice, so it is expected that treatment by individual doctors will vary depending on their interpretation of the guideline. Nevertheless, the improved guideline should be suitable for Japanese patients and useful for conscientious management of *H. pylori* infection.

Conclusion

Whether or not *H. pylori* eradication therapy can suppress gastric cancer has been a serious issue in this field. New

evidence obtained from our study in Japan may be helpful worldwide.
for the prevention and eventual elimination of gastric cancer

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