Acknowledgements and Funding
This work was supported in part by a grant from Chiyoda Mutual Life Foundation, and was also supported in part by a grant from St Luke's Life Science Institute. This work is dedicated to the memory of Dr. Tomoyoshi Kanayama, a previous medical chief of Health Department, Human Resources Division, Nippon Steel Corporation, who is sadly missed.

Author details
[1]Department of Gastroenterology, Graduate School of Medicine, University of Tokyo (7-3-1, Hongo, Bunkyo-ku, Tokyo, Japan. [2]Health Department, Human Resources Division, Nippon Steel Corporation (2-6-1, Marunouchi, Chiyoda-ku, Tokyo, Japan. [3]Department of Gastroenterology, School of Medicine, Wakayama Medical University (811-1, Kimiidera, Wakayama-shi, Wakayama, Japan.

Authors' contributions
Author's contributions were as follows: NY (study concept and design, acquisition of data, analysis and interpretation of data, statistical analysis, drafting of the manuscript), TS (analysis and interpretation of data, statistical analysis), CM (analysis and interpretation of data), YY (acquisition of data), MF (administrative support), SK (acquisition of data), JK (analysis and interpretation of data), OG (acquisition of data), SO (acquisition of data), KN (acquisition of data), YT (analysis and interpretation of data), MK (acquisition of data), MI (critical revision of the manuscript for important intellectual content, drafting of the manuscript), and KK (study supervision). The final manuscript has been carefully read and approved by all the authors.

Competing interests
The authors declare that they have no competing interests.

Received: 14 August 2011 Accepted: 21 December 2011
Published: 21 December 2011

References

1. Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, Stanghellini V: **Functional gastroduodenal disorders.** *Gastroenterology* 2006, **130(5)**:1466-1479.
2. Drossman DA: **The functional gastrointestinal disorders and the Rome III process.** *Gastroenterology* 2006, **130(5)**:1377-1390.
3. McColl K, Murray L, El-Omar E, Dickson A, El-Nujumi A, Wirz A, Kelman A, Penny C, Knill-Jones R, Hilditch T: **Symptomatic benefit from eradicating Helicobacter pylori infection in patients with nonulcer dyspepsia.** *N Engl J Med* 1998, **339(26)**:1869-1874.
4. Blum AL, Talley NJ, O'Morain C, van Zanten SV, Labenz J, Stolte M, Louw JA, Stubberod A, Theodors A, Sundin M, *et al*: **Lack of effect of treating Helicobacter pylori infection in patients with nonulcer dyspepsia. Omeprazole plus Clarithromycin and Amoxicillin Effect One Year after Treatment (OCAY) Study Group.** *N Engl J Med* 1998, **339(26)**:1875-1881.
5. Talley NJ, Vakil N, Ballard ED, Fennerty MB: **Absence of benefit of eradicating Helicobacter pylori in patients with nonulcer dyspepsia.** *N Engl J Med* 1999, **341(15)**:1106-1111.
6. Heaney A, Collins JS, Watson RG, McFarland RJ, Bamford KB, Tham TC: **A prospective randomised trial of a "test and treat" policy versus endoscopy based management in young Helicobacter pylori positive patients with ulcer-like dyspepsia, referred to a hospital clinic.** *Gut* 1999, **45(2)**:186-190.
7. Marzio L, Cappello G, Ballone E: **Evaluation of dyspeptic symptoms in patients with and without Helicobacter pylori infection and normal upper gastrointestinal endoscopy.** *Dig Liver Dis* 2003, **35(3)**:138-142.
8. Karamanolis G, Caenepeel P, Arts J, Tack J: **Association of the predominant symptom with clinical characteristics and pathophysiological mechanisms in functional dyspepsia.** *Gastroenterology* 2006, **130(2)**:296-303.
9. Sohn J, Levine MS, Furth EE, Laufer I, Rubesin SE, Herlinger H, Lichtenstein GR: **Helicobacter pylori gastritis: radiographic findings.** *Radiology* 1995, **195(3)**:763-767.
10. Dheer S, Levine MS, Redfern RO, Metz DC, Rubesin SE, Laufer I: **Radiographically diagnosed antral gastritis: findings in patients with and without Helicobacter pylori infection.** *Br J Radiol* 2002, **75(898)**:805-811.
11. Marciani L, Gowland PA, Fillery-Travis A, Manoj P, Wright J, Smith A, Young P, Moore R, Spiller RC: **Assessment of antral grinding of a model solid meal with echo-planar imaging.** *Am J Physiol Gastrointest Liver Physiol* 2001, **280(5)**:G844-849.
12. Marciani L, Gowland PA, Spiller RC, Manoj P, Moore RJ, Young P, Fillery-Travis AJ: **Effect of meal viscosity and nutrients on satiety, intragastric dilution, and emptying assessed by MRI.** *Am J Physiol Gastrointest Liver Physiol* 2001, **280(6)**:G1227-1233.
13. Sasazuki S, Inoue M, Iwasaki M, Otani T, Yamamoto S, Ikeda S, Hanaoka T, Tsugane S: **Effect of Helicobacter pylori infection combined with CagA and pepsinogen status on gastric cancer development among Japanese men and women: a nested case-control study.** *Cancer Epidemiol Biomarkers Prev* 2006, **15(7)**:1341-1347.
14. Kusano M, Shimoyama Y, Sugimoto S, Kawamura O, Maeda M, Minashi K, Kuribayashi S, Higuchi T, Zai H, Ino K, *et al*: **Development and evaluation of FSSG: frequency scale for the symptoms of GERD.** *J Gastroenterol* 2004, **39(9)**:888-891.
15. Matsuda R, Morizane T, Tsunematsu S, Kawana I, Tomiyama M: **Helicobacter pylori prevalence in dentists in Japan: a seroepidemiological study.** *J Gastroenterol* 2002, **37(4)**:255-259.
16. Asaka M, Sugiyama T, Nobuta A, Kato M, Takeda H, Graham DY: **Atrophic gastritis and intestinal metaplasia in Japan: results of a large multicenter study.** *Helicobacter* 2001, **6(4)**:294-299.
17. Deutsch JA, Young WG, Kalogeris TJ: **The stomach signals satiety.** *Science* 1978, **201(4351)**:165-167.
18. Deutsch JA: **The role of the stomach in eating.** *Am J Clin Nutr* 1985, **42(5 Suppl)**:1040-1043.
19. Deutsch JA, Jang Ahn S: **The splanchnic nerve and food intake regulation.** *Behav Neural Biol* 1986, **45(1)**:43-47.
20. Distrutti E, Azpiroz F, Soldevilla A, Malagelada JR: **Gastric wall tension determines perception of gastric distention.** *Gastroenterology* 1999, **116(5)**:1035-1042.
21. Tack J, Coulie B, Wilmer A, Andrioli A, Janssens J: **Influence of sumatriptan on gastric fundus tone and on the perception of gastric distension in man.** *Gut* 2000, **46(4)**:468-473.
22. Schirra J, Wank U, Arnold R, Goke B, Katschinski M: **Effects of glucagon-like peptide-1(7-36)amide on motility and sensation of the proximal stomach in humans.** *Gut* 2002, **50(3)**:341-348.
23. Delgado-Aros S, Cremonini F, Castillo JE, Chial HJ, Burton DD, Ferber I, Camilleri M: **Independent influences of body mass and gastric volumes on satiation in humans.** *Gastroenterology* 2004, **126(2)**:432-440.
24. Mukoubayashi C, Yanaoka K, Ohata H, Arii K, Tamai H, Oka M, Ichinose M: **Serum pepsinogen and gastric cancer screening.** *Intern Med* 2007, **46(6)**:261-266.

Pre-publication history
The pre-publication history for this paper can be accessed here:
http://www.biomedcentral.com/1471-230X/11/140/prepub

doi:10.1186/1471-230X-11-140
Cite this article as: Yamamichi *et al.*: Postprandial fullness correlates with rapid inflow of gastric content into duodenum but not with chronic gastritis. *BMC Gastroenterology* 2011 11:140.

厚生労働科学研究費補助金

がん臨床研究事業

ピロリ菌除菌による胃癌予防の経済評価に関する研究

平成２２年度～２４年度　総合研究報告書

研究代表者　加藤　元嗣

平成２５（２０１３）年　５月

２／２冊

「研究成果の刊行に関する別刷り」

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2012;42(11)987–994
doi:10.1093/jjco/hys151
Advance Access Publication 26 September 2012

Review Article

Recent Development of Gastric Cancer Prevention

Mototsugu Kato[1,*] and Masahiro Asaka[2]

[1]Division of Endoscopy, Hokkaido University Hospital and [2]Department of Cancer Preventive Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

*For reprints and all correspondence: Mototsugu Kato, Division of Endoscopy, Hokkaido University Hospital, North 14, West 5, Kita-ku, Sapporo, Hokkaido 060-8468, Japan. E-mail: m-kato@med.hokudai.ac.jp

Received February 27, 2012; accepted August 21, 2012

A mass screening program using photofluorography has been used as a secondary prophylaxis of gastric cancer in Japan. However, we are at a turning point for reconsidering the strategy of gastric cancer prevention because of various problems with photofluorography. The shift from current secondary prophylaxis to primary prophylaxis is now required. After a Japanese multicenter randomized controlled trial showed that *Helicobacter pylori* eradication reduced the incidence of metachronous gastric cancer after endoscopic resection of early gastric cancer, primary prophylaxis of gastric cancer has gained greater attention. The combination of *H. pylori* eradication as a primary prophylaxis and screening as a secondary prophylaxis is necessary for the elimination of gastric cancer in Japan. The strategy of test, treat and screening for *H. pylori* infection is effective in reducing the incidence and mortality of gastric cancer in communities with a high incidence of gastric cancer. We have proposed a program of risk stratification based on the presence of *H. pylori* infection with or without atrophic gastritis followed by targeted interventions.

Key words: screening – photofluorography – endoscopy – pepsinogen – H. pylori *eradication*

INTRODUCTION

The final goal of cancer prevention is to reduce cancer incidence and mortality. Cancer prevention consists of primary and secondary prophylaxes. Primary prophylaxis includes avoiding exposure to known cancer-causing agents, enhancement of host-defensive mechanisms, modifying life style and chemoprevention (1). Secondary prophylaxis consists of screening and treatment for early stage of cancer.

Although the age-adjusted mortality of gastric cancer has decreased in the last few decades, gastric cancer is the second leading cause of death from cancer in Japan (2). Gastric cancer accounted for 12.5% of ~344 000 cancer deaths in 2009. Mass screening for gastric cancer has been conducted nationwide for all residents aged 40 years and over since 1983 under the Health Service Law for the Aged (3). Photofluorography using a barium meal has been the main screening method for gastric cancer. The purpose of cancer screening includes the detection of gastric cancer in its early stage and intervention in its natural development through appropriate treatment. However, the evidence that *Helicobacter pylori* (*H. pylori*) eradication prevents the development of metachronous gastric cancer after endoscopic resection of primary gastric cancer was provided through a Japanese multicenter randomized controlled trial (4). Ideally, removal of the cause of the cancer before its occurrence will become part of the strategy of primary prevention of gastric cancer.

PRIMARY PREVENTION OF GASTRIC CANCER

The methodology of primary cancer prevention has an epidemiological approach and a chemical approach. The epidemiological approach includes the elucidation of

cancer-causing agents and cancer-preventive agents among foods, drinks and modern living habits in developed countries. The aim of the epidemiological approach is to reduce cancer incidence and mortality by exclusion of causal factors and supplementation of preventive factors that are associated with anti-carcinogenesis. Dietary salt intake, refraining from smoking and consumption of vegetables and fruits are known as preventive methods in the field of nutrition (5). The chemical approach includes chemoprevention for inhibition of cancer using various chemicals. The aim of the chemical approach is to exterminate causal microorganism and to stop cancer development using the administration of chemical substances that have direct anti-carcinogenesis. Eradication treatment of *H. pylori* infection using antimicrobial agents and non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin are used as chemoprevention for gastric cancer (1).

Diet and Nutrition

The World Cancer Research Fund and the American Institute for Cancer Research issued a report about food, nutrition, physical activity and the prevention of cancer in 2007 (6). In this expert study, causal factors and preventive factors for gastric cancer were analyzed from many studies as shown below. Non-starchy vegetables, particularly allium vegetables, as well as fruits probably protect against stomach cancer. Salt and also salt-preserved foods are probably the causes of this cancer. Limited evidence suggests that pulses, including soya and soya products, and also foods containing selenium protect against stomach cancer. There is also limited evidence suggesting that chilis, processed meat, smoked foods and grilled (broiled) and barbecued (char-broiled) animal flesh are causes of stomach cancer. Infection with the bacterium *H. pylori* has been established as a necessary cause of almost all cases of gastric cancer. It has been estimated that most cases of this cancer are preventable through appropriate diet and associated factors.

Trends in age-standardized incidence and mortality of gastric cancer worldwide have declined in the last few decades. The most likely reason for this trend is a marked change in the life style. A reduced intake of salted, pickled and preserved foods, increased consumption of fruit and vegetables and widespread use of refrigeration contributed to decline in gastric cancer incidence (7). An animal model study demonstrated the dose-dependent enhancing effects of salt in gastric chemical carcinogenesis in *H. pylori*-infected Mongolian gerbils associated with the alteration of the mucous microenvironment (8). However, the enhancing effects of salt were not found in *H. pylori*-negative Mongolian gerbils. A reduction in salt intake has the possibility of preventing gastric carcinogenesis in *H. pylori*-infected patients.

Consumption of fresh fruits and vegetables was reported to have a significant reduction in gastric cancer risk in several prospective studies. 10 years of follow-up of the Japan Public Health Center study cohort showed that the intake one or more days per week of yellow vegetables, white vegetables and fruit reduced gastric cancer risk compared with <1 day per week (9). In the meta-analysis of relevant published cohort studies until 2004, an inverse association was observed between fruit intake and gastric cancer incidence (relative risk (RR): 0.82; 95% confidence interval (CI): 0.73–0.93) and this was stronger for follow-up periods of >10 years (RR: 0.66; 95% CI: 0.52–0.83) (10). For vegetables, the relative rate was significantly reduced to 0.71 (95% CI: 0.53–0.94) when considering only those with the longer follow-up. Vegetables and fruits include those rich in nutrients such as ascorbic acid, carotenoid and beta-carotene that may be protective against gastric carcinogenesis. Ascorbic acid is an important anti-oxidant that inhibits tumor cell mitotic activity without affecting normal cell growth (11). Carotenoid is also a powerful anti-oxidant that protects against damage caused by free radicals (12). Because beta-carotene, a precursor of retinol, has anti-cancer effects, it is expected to prevent gastric carcinogenesis (13). Green tea contains polyphenols, more commonly known as catechins. Catechins include epigallocatechin-3-gallate that was proved to inhibit carcinogenesis in both *in vitro* and *in vivo* studies (14,15). However, these epidemiological associations do not establish beyond doubt that dietary interventions will reduce gastric cancer incidence.

Chemoprevention

NSAIDs including aspirin possess the action which obstructs cyclo-oxygenase-2 (COX-2). The expression of COX-2 has been detected not only in colon cancer but also in other organ cancers. Chemoprevention using COX-2 inhibitors has been investigated in every organ. The overexpression of COX-2 is strongly found in non-cardiac cancer and well-differentiated stomach cancer. The preventive effect of NSAIDs for gastric cancer has been observed in some animal model experiments.

The results from a cohort study and a meta-analysis showed that the use of any aspirin reduced significantly the risk of non-cardiac cancer [hazard ratio (HR): 0.64, 95% CI: 0.47–0.86], but no inhibition of cardiac cancer risk (HR: 0.82, 95% CI: 0.67–1.04) (16). The use of other NSAIDs reduced significantly the risk of non-cardiac cancer (HR: 0.68, 95% CI: 0.57–0.81) and cardiac cancer (HR: 0.80, 95% CI: 0.67–0.95). Multivariate analysis of a nationwide retrospective cohort study in Taiwan suggested that regular NSAID use was an independent protective factor for gastric cancer development (HR: 0.79, 95% CI: 0.69–0.90) (17). Long-term administration of selective COX-2 inhibitor reduced the incidence of metachronous cancer development after endoscopic resection of early gastric cancer with the same degree of effectiveness as *H. pylori* eradication (18). Although NSAIDs are one of the candidate agents for chemoprevention of gastric cancer, the safety of long-term

Table 1. Japanese cohort studies of *H. pylori* eradication and gastric cancer development

Author	Year	*n* (disease)	Group	Follow (years)	Incident rate of GCA (%)	Incident rate per year (%)	Significance (per protocol)
Take	2005	1342 (GU/DU)	C	3.4	4/176 (2.3)	0.68	$P < 0.01$
			E	3.4	8/944 (0.8)	0.24	
Takenaka	2007	1807 (GU/DU)	C	2.9	5/288 (1.7)	0.59	$P < 0.05$
			E	3.3	6/1519 (0.4)	0.12	
Ogura	2008	708 (GU/DU)	C	3.1	13/304 (4.3)	1.40	$P < 0.01$
			E	3.2	6/404 (1.5)	0.47	
Yanaoka	2009	4141 (Healthy)	C	9.3	55/3658 (1.5)	0.16	n.s
			E	9.3	5/473 (1.1)	0.12	
Mabe	2009	4133 (GU/DU)	C	5.2	9/352 (2.6)	0.50	$P < 0.05$
			E	5.6	47/3781 (1.2)	0.21	

GU, gastric ulcer; DU, duodenal ulcer; C, control; E, eradication; GCA, gastric cancer.

Table 2. Randomized controlled studies of *H. pylori* eradication and gastric cancer development

Author	Year	*n* (disease)	Follow (years)	Group	Incident rate of GCA (%)	Incident rate per year (%)	Significance
Correa	2000	967 (Healthy)	6	C	2/485 (0.4)	0.07	n.s.
				E	3/491 (0.6)	0.10	
Wong	2004	1807 (Healthy)	7.5	C	11/813 (1.4)	0.18	n.s.
				E	7/817 (0.9)	0.11	
You	2006	2258 (Healthy)	7.3	C	27/1128 (2.4)	0.33	n.s.
				E	19/1130 (1.7)	0.23	
Saito	2005	692 (Healthy)	4	C	3/313 (1.0)	0.24	n.s.
				E	2/379 (0.5)	0.13	
Zhou	2008	552 (Healthy)	8	C	7/276 (2.5)	0.32	n.s.
				E	2/276 (0.7)	0.09	
Fukase	2008	505 (Resected GCA)	3	C	24/255 (9.4)	3.1	$P < 0.01$
				E	9/250 (3.6)	1.2	

have mucosal atrophy and intestinal metaplasia. A recent retrospective study about metachronous gastric cancer after endoscopic resection of early gastric cancer showed that the rates of metachronous cancer were 14.3% in the persistent group and 8.5% in the eradicated group (35). Although *H. pylori* eradication significantly suppressed the incidence of metachronous cancer at 5 years of follow-up, there was no significant difference during the overall follow-up period. Because the median follow-up period in a retrospective study was 3.0 years, it seems that >5 years follow-up period based on a small sample size and great uncertainty. To determine the long-term effect of *H. pylori* eradication on the development of gastric cancer, the long-term follow-up analysis of this randomized controlled study was necessary. In the mean 5 years follow-up period, metachronous gastric carcinoma had developed in 22 patients in the eradication group and 43 in the control group (HR: 0.497; $P = 0.008$) (presentation in DDW2012). This result suggested that *H. pylori* eradication prevented the development of metachronous gastric cancers after endoscopic resection during a long-term follow-up. Since participants in this study had a history of gastric cancer, one would expect that they differ from the general population in terms of specific genotypes and environmental factors. Although this could limit the generalizability of the results, the positive data support the use of *H. pylori* eradication to prevent the development of gastric cancer.

Helicobacter pylori infection has the possibility of both initiating and promoting the development of gastric cancer (36). It seems that *H. pylori* eradication almost completely suppresses the incidence of gastric cancer before carcinomatous change of cell develops. The potential effect of *H. pylori* eradication on latent cancer (defined as tiny cancers due to chronic *H. pylori* infection that cannot be

NSAID use is required for chemoprevention with NSAIDs in general population.

H. pylori Eradication

Gastric carcinogenesis is a multi-factorial process including environmental factors, socioeconomic conditions and living habits. However, almost all gastric cancers including both intestinal type and diffuse type arise from the mucosa infected by *H. pylori*, and these tumors very rarely arise from gastric mucosa without inflammation. *H. pylori* plays the most important role in gastric carcinogenesis (19). In experimental research in which cancer was induced in Mongolian gerbils through *H. pylori* inoculation plus administration of low-dose chemical carcinogens, *H. pylori* eradication suppressed the incidence of gastric cancer (20). The animal experiment also suggested that eradication at an earlier period was effective as reducing gastric carcinogenesis compared with that at the middle or late period (21).

Cohort Study

Five Japanese cohort studies, in which the eradicated and non-eradicated subjects underwent endoscopic follow-up to assess the development of gastric cancer, have been reported (22–26). The results of four cohort studies for peptic ulcer patients have suggested an inhibitory effect of *H. pylori* eradication on gastric cancer incidence using per protocol analysis. One cohort study based on an employer-sponsored medical examination did not have significant results during 9 years of follow-up using X-ray examination. These different results depended on the incidence rates of gastric cancer (Table 1). The incidence rates of gastric cancer in studies with significant results are higher than those of studies without significant results. A large-scale retrospective cohort study in Taiwan showed that early *H. pylori* eradication is associated with decreased risk of gastric cancer in patients with peptic ulcer diseases (HR:0.78, :95% CI: 0.60–0.99) (27). Since 1-year difference in eradication timing affects the incidence rate of gastric cancer, early eradication is crucial. Most of the positive cohort data of gastric cancer prevention by *H. pylori* eradication was investigated in the subjects with peptic ulcer. Patients with especially gastric ulcer have a higher risk of gastric cancer incidence than the general population. One cohort study without peptic ulcer showed that a significant reduction in cancer incidence after eradication was observed only in pepsinogen (PG) test-negative subjects with a mild atrophic change (25). To confirm these cohort results, a randomized controlled study based on the general population is necessary.

Randomized Controlled Study

A double-blind randomized study in China showed that gastric cancer still occurred after successful eradication of *H. pylori* and that *H. pylori* eradication did not lead to significant decrease in the incidence of gastric cancer (28). In the Fujian Province, where the mortality rate due to gastric cancer is high, 1 630 people with *H. pylori* infection were randomly assigned to an *H. pylori* eradication therapy group or a placebo group, and were followed for 7.5 years. During the follow-up, the development of gastric cancer was observed in 7 subjects from the *H. pylori* eradication therapy group and 11 subjects from the placebo group, with no significant difference between the two 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 ($P = 0.02$). This study suggested that the preventive effect of *H. pylori* eradication for gastric cancer is sufficient only in patients without an atrophic change.

Meta-analysis of five randomized controlled studies that compared eradication treatment with no treatment in *H. pylori*-positive patients was reported whether *H. pylori* eradication treatment reduce the incidence of primary gastric cancer (29–33). Over a follow-up period ranging from 4 to 10 years, 33 of 3 112 patients (1.0%) who received eradication treatment developed gastric cancer compared with 50 of 3 031 controls (1.6%). This difference yielded an RR of 0.65 (95% CI: 0.42–1.01) ($P = 0.05$) (34). Interventional studies to investigate the preventive effect of primary gastric cancer require a large sample number and a long-term observation period in order to get significant results (Tables 2 and 3).

Metachronous Cancer after Endoscopic Resection

Mucosal gastric cancer is usually resected by endoscopic treatment in Japan. Metachronous gastric cancer after endoscopic resection of primary gastric cancer often develops at another site within the stomach. The incidence rate of metachronous cancer rate has ranged from 2.5 to 14% for different follow-up periods. A large-scale, multi-center, randomized controlled open-label study was conducted to determine whether the eradication of *H. pylori* had inhibitory effects on the development of metachronous gastric carcinomas after endoscopic resection (4). The 542 subjects were randomly allocated to an eradication arm ($n = 271$) and control arm ($n = 271$) and examined endoscopically during 3 years. Metachronous gastric cancer developed in 33 cases, including 9 in the eradication group and 24 in the control group. The incidence of metachronous gastric cancer in the eradication group was significantly lower than that in the control group, even in the analysis ignoring the observation period (HR: 0.34, 95% CI: 0.16–0.70, $P = 0.003$). Overall results show that *H. pylori* eradication reduces the risk of developing new gastric cancer even in the highest risk group. Sub-analysis of previous papers showed that the preventive effect of *H. pylori* eradication for gastric cancer incidence was limited to patients without atrophy and metaplasia (25,28). However, based on the results of this study, *H. pylori* eradication may also be effective in patients who

Table 3. Incidence rate of gastric cancer and sample size

	Primary gastric cancer	Metachronous gastric cancer
Subjects	*H. pylori* positive	*H. pylori* positive after endoscopic resection of primary cancer
Incident rate/year (%)		
Control group	0.2–0.4	3–5
Eradication group	0.1–0.2	1–2
Sample size	10 000	500
Follow-up period	10 years	3 years

detected by endoscopy) is not only to slow its growth, but also to almost completely suppress it (zero growth), or to suppress it completely (negative growth) (37).

SECONDARY PREVENTION OF GASTRIC CANCER

The 5 year survival rate of early stage gastric cancer is >95% according to the progression of gastric cancer treatment in Japan (38). Since the stage of gastric cancer at the time of detection correlates with the prognosis, secondary prevention is important for early detection and early treatment. The aim of secondary prophylaxis is to detect gastric cancer in its early stage and to protect its natural development through appropriate treatment. The present method of gastric cancer screening is an indirect or direct barium meal X-ray examination, a serum PG check and endoscopic examination (Table 4). The Japanese Research Group for Cancer Screening Guidelines developed the guidelines in 2006 based on the evaluation of efficacies of various methods for cancer screening (39). Although there was no randomized controlled study that used photofluorography in gastric cancer screening, the reduction in mortality from gastric cancer was found in five case–control studies, one cohort study and meta-analysis. Therefore, gastric cancer screening using photofluorography is recommended for population-based and opportunistic screening in Japan (40). At the same time, no other methods are recommended for gastric cancer screening. However, in spite of many problems in current gastric cancer screening using photofluorography, there is increasing support for gastric cancer screening using endoscopy, serum PG and *H. pylori* antibody. Since the number of gastric cancer deaths has not decreased in Japan, it is not advisable to incorporate the use of photofluorography into the current mass screening program (41).

X-Ray Examination

The barium meal indirect X-ray examination using double-contrast radiography was introduced as a mass screening program of gastric cancer in the 1960 s in Japan (3). It is

Table 4. Method of gastric cancer screening

	Photofluography	Endoscopy	Pepsinogen
Indication	Population based	Opportunistic	Population based
Secondary screening	Endoscopy	Not necessary	Endoscopy
Participants	~6 390 000	~210 000	~500 000
Detection rate of gastric cancer	0.088%	0.30%	0.44%
Evidence of mortality reduction	Case–control study meta-analysis	Case–control study	Case–control study
Level of evidence (minds)	Evidence level IVa	Evidence level IVa	Evidence level IVa

used widely in resident medical examination by municipal districts under the Health Service Law for the aged, employer medical examination and personal medical examination. Gastric cancer screening using photofluorography indicated the reduction of mortality in meta-analysis including three Japanese case–control studies, but its evidence level is not strong, i.e. equivalent to IVa in the MINDS (Medical Information Network Distribution Service) classification (42). The sensitivity of photofluorography ranged from 60 to 80%, whereas the specificity and true positive rate were 90 and 0.7–2.0%, respectively. In overall results of Japanese cancer screening in 2007, the number of persons who received gastric cancer screening using photofluorography and the number of detected gastric cancers were about 6 390 000 and 5600, respectively. However, endoscopic examination as close examination found gastric cancer at a different site in the half of screen-detected gastric cancers. True detection rate of early gastric cancer using photofluorography is known to be not so high. Current gastric cancer screening using photofluorography has various well-known problems, such as low consultation rate of close examination and immobilization of participant. Recently, the prevalence rate of *H. pylori* infection in <50-year old Japanese has decreased to <40% (43). Since more than half of participants in gastric cancer screening have low risk of gastric cancer, it is a serious problem that *H. pylori* negative persons have to receive photofluorography every year in terms of radiation exposure. Unnecessary annual invasive screening examinations for *H. pylori*-negative population should be avoided. Therefore, it is necessary to reconsider the mass screening program of gastric cancer using photofluorography.

Endoscopic Examination

Recently, endoscopic screening for gastric cancer has been used gradually according to the spread of transnasal esophagogastroduodenoscopy (44). Transnasal endoscopy is suitable for gastric cancer screening because of good

compliance by participants (45,46). Mass screening using endoscopic examination has some problems such as the need for an endoscopist, performance limitation of operation number, sterilization of scope, complication of endoscopy and low acceptability of participant. Endoscopic examination has been the best for finding early gastric cancer, with a detection ratio of 0.87% in 2004, approximately about three to five times higher than those of photofluorography (47). The efficacy of endoscopic screening in terms of mortality reduction in Japan has been compared with that of X-ray examination (48): 4261 residents underwent gastric X-ray examination for gastric cancer screening from 1991 to 1995, and all 7178 residents underwent endoscopic examination for the same purpose from 1996 to 2003. Following the introduction of endoscopic screening, the age-adjusted gastric cancer mortality rates decreased from 1.04 (95% CI: 0.50–1.58) to 0.71 (95% CI: 0.33–1.10) for males and from 1.54 (95% CI: 0.71–2.38) to 0.62 (95% CI: 0.19–1.05) for females. Reduction of gastric cancer mortality was achieved by not only increase in the detection of early cancer using endoscopic screening but also improvement in the treatment including surgery.

Serum Pepsinogen Test

PG is a precursor for pepsin produced in the gastric mucosa, of which 99% is secreted into the gastric lumen and 1% into the blood stream. PG is classified into two biochemically and immunologically different isozymes, namely PG I and PG II. While PG I is produced in chief and mucous neck cells of fundic glands, PG II is secreted from the fundic, pyloric and proximal duodenal glands (49,50). Serum PG level reflects the morphology and function of acid secretary glands and pathological condition of gastric mucosa such as inflammation (51–53). The inflammation of gastric mucosa by *H. pylori* infection elevates serum PG I and PG II levels and decreases PG I/II ratios due to relative high elevation of PG II. A decline in serum PG I levels and PG I/II ratios correlates with the extent of mucosal atrophy in the gastric corpus and gastric acid secretion ability. Stepwise reduction in the PG I/II ratio is closely correlated with the progression from normal gastric mucosa to extensive atrophic gastritis (54,55).

The risk of gastric cancer incidence, especially the intestinal type, depends on the advancement of atrophic gastritis. Serum PG level is considered a useful marker of atrophic gastritis, which is a precancerous change in the stomach. Mass screening of high-risk patients with gastric cancer using the PG method was introduced to detect gastric cancer following endoscopic examination. Positive PG method that are PG I $\leq$70 ng/l and PG I/II ratio $\leq$3.0 indicates high risk of gastric cancer. Prospective cohort studies also confirmed that the PG method is useful for assessing gastric cancer risk (56–58). A case–control study on the effect of gastric cancer screening using the PG method showed the odds ratios for death from gastric cancer among control subjects screened within 1 and 2 years were 0.238 (0.061–0.929) and 0.375 (0.155–0.905), respectively (59). Gastric cancer screening using the PG method was suggested to reduce mortality from gastric cancer.

The ABC(D) stratification using both anti-*H. pylori* antibody and serum PG levels allows the classification of gastric cancer risk into the following groups based on these levels: Group A is negative for both PG method results and the antibody, Group B is negative for PG method results and positive for the antibody, Group C is positive for both PG method results and the antibody and Group D that is positive for PG method results and negative for the antibody. With the progression of *H. pylori*-induced gastritis, the risk of gastric cancer increased in a stepwise fashion from Group B (HR = 7.13, 95% CI = 0.95–53.33) to Group C (HR = 14.85, 95% CI = 1.96–107.7) and finally to Group D (HR = 61.85, 95% CI = 5.6–682.64) (60). In another result, Group C had a moderately high HR of 11.23, while Group D had a markedly higher HR of 14.81 (61). Therefore, these two groups are considered the most appropriate candidates for gastric cancer screening. Recently, ABC(D) stratification has spread as a new method of gastric cancer screening (Table 5). Because of the high risk of gastric cancer, endoscopic examination is recommended every year for Group D, every 2 years for Group C, every 3 years for Group B and every 5 years for Group A (62).

STRATEGY OF ELIMINATING GASTRIC CANCER

According to Asia-Pacific consensus guidelines, a population 'test-and-treat' strategy for *H. pylori* infection in communities with a high incidence of gastric cancer such as Japan and Korea is considered to be an effective strategy for gastric cancer prevention (63,64). The Japanese Society for *Helicobacter* Research has published a guideline recommending that *H. pylori* infection be treated with eradication therapy (42) The strategy of test and treat for *H. pylori* infection is effective at reducing the incidence and mortality of gastric cancer in communities with a high incidence of gastric cancer. However, the follow-up surveillance for

Table 5. The ABC(D) stratification

Group	A	B	C	D
Anti-*H. pylori* antibody	Negative	Positive	Positive	Negative
Pepsinogen method	Negative	Negative	Positive	Positive
Risk of gastric cancer	Low	⟶	⟶	High
Odds rate	1.00	4.20	11.23	14.81
Interval of endoscopy	Every 5 years	Every 3 years	Every 2 years	Every 1 year

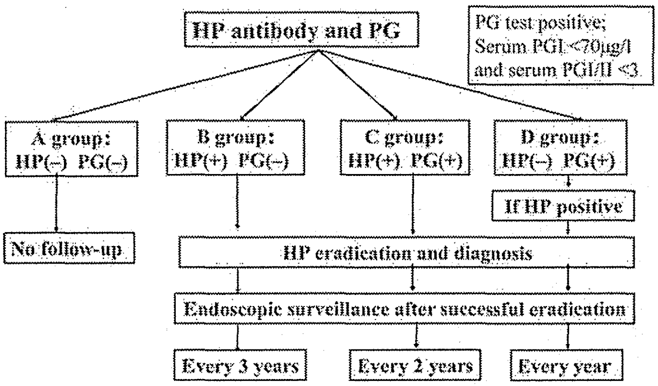

Figure 1. The strategy for elimination of gastric cancer.

gastric cancers was necessary after successful eradication of *H. pylori*, because the risk of cancer persists for long after cure of *H. pylori*. Therefore, the strategy of test, treat and screening that combines primary and secondary prophylaxes is the most important to reach the final goal of eliminating gastric cancer in Japan.

We have proposed a program of risk stratification (ABC stratification) based on the presence of *H. pylori* infection with or without atrophic gastritis followed by targeted interventions (41) (Fig. 1) Those at no risk for gastric cancer (no *H. pylori*, no atrophic gastritis) need no therapy or follow-up. Those at low risk (*H. pylori* infected, non-atrophic gastritis) need only *H. pylori* eradication therapy. The smaller groups at high or very high risk need eradication and cancer surveillance using the endoscopic examination. We estimated the costs and the benefits of this strategy markedly reduce the cost of treating gastric cancer in spite of initially increasing national healthcare expenditure. In Japan, ~3 billion dollars are spent annually on the treatment of gastric cancer (65). The annual cost will probably exceed 5 billion dollars after 10 years if an effective strategy of gastric cancer prevention is not taken. Theoretically, the eradication of *H. pylori* in all carriers could prevent ~150 000 deaths from gastric cancer during the subsequent 5 years (66). The program of gastric cancer prevention is expected to induce reduction in costs consumed by *H. pylori*-related diseases.

One week of triple therapy using a proton pump inhibitor (PPI) combined with amoxicillin (AMPC) and clarithromycin (CAM) is used as the first-line treatment for eradicating *H. pylori* in Japan. If the first-line treatment is failed, 1 week of triple therapy including PPI, AMPC and metronidazole is used as the second-line rescue treatment. Overall the eradication rate of first- and second-line treatment is currently 97–98%. Because adverse events are mainly soft stools and diarrhea, the safety of *H. pylori* eradication treatment is proved.

Conflict of interest statement

None declared.

References

1. Kakizoe T. Chemoprevention of cancer—focusing on clinical trials. *Jpn J Clin Oncol* 2003;33:421–42.
2. Inoue M, Tsugane S. Epidemiology of gastric cancer in Japan. *Postgrad Med J* 2005;81:419–24.
3. Hisamichi S, Sugawara N. Mass screening for gastric cancer by X-ray examination. *Jpn J Clin Oncol* 1984;11:211–33.
4. Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008;372:392–7.
5. Tsugane S, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence. *Gastric Cancer* 2007;10:75–83.
6. Wiseman M. The Second World Cancer Research Fund/American Institute for Cancer Research Expert Report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. *Proc Nutr Soc* 2008;67:253–6.
7. Palli D. Epidemiology of gastric cancer. *Ann Ist Super Sanita* 1996;32:85–99.
8. Kato S, Tsukamoto T, Mizoshita T, et al. High salt diets dose-dependently promote gastric chemical carcinogenesis in Helicobacter pylori-infected Mongolian gerbils associated with a shift in mucin production from glandular to surface mucous cells. *Int J Cancer* 2006;119:1558–66.
9. Kobayashi M, Tsubono Y, Sasazuki S, Sasaki S, Tsugane S., JPHC Study Group. Vegetables, fruit and risk of gastric cancer in Japan: a 10-year follow-up of the JPHC Study Cohort I. *Int J Cancer* 2002;102:39–44.
10. Lunet N, Lacerda-Vieira A, Barros H. Fruit and vegetables consumption and gastric cancer: a systematic review and meta-analysis of cohort studies. *Nutr Cancer* 2005;53:1–10.
11. Poydock ME, Fardon JC, Gallina D, Ferro V, Heher C. Inhibiting effect of vitamins C and B12 on the mitotic activity of ascites tumors. *Exp Cell Biol* 1979;47:210–7.
12. Palace VP, Khaper N, Qin Q, Singal PK. Antioxidant potentials of vitamin A and carotenoids and their relevance to heart disease. *Free Radic Biol Med* 1999;26:746–61.
13. Rousseau EJ, Davison AJ, Dunn B. Protection by beta-carotene and related compounds against oxygen-mediated cytotoxicity and genotoxicity: implications for carcinogenesis and anticarcinogenesis. *Free Radic Biol Med* 1992;13:407–33.
14. Wang ZY, Cheng SJ, Zhou ZC, Athar M, Khan WA, Bickers DR. Antimutagenic activity of green tea polyphenols. *Mutat Res* 1989;223:273–85.
15. Xu Y, Ho CT, Amin SG, Han C, Chung FL. Inhibition of tobacco specific nitrosamine-induced lung tumorigenesis in A/J mice by green tea and its major polyphenols as antioxidants. *Cancer Res* 1992;52:3875–9.
16. Abnet CC, Freedman ND, Kamangar F, Leitzmann MF, Hollenbeck AR, Schatzkin A. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. *Br J Cancer* 2009;100:551–7.
17. Wu CY, Wu MS, Kuo KN, Wang CB, Chen YJ, Lin JT. Effective reduction of gastric cancer risk with regular use of nonsteroidal anti-inflammatory drugs in Helicobacter pylori-infected patients. *J Clin Oncol* 2010;28:2952–7.
18. Yanaoka K, Oka M, Yoshimura N, et al. Preventive effects of etodolac, a selective cyclooxygenase-2 inhibitor, on cancer development in extensive metaplastic gastritis, a Helicobacter pylori-negative precancerous lesion. *Int J Cancer* 2010;126:1467–73.
19. Kato M, Asaka M. Recent knowledge of the relationship between Helicobacter pylori and gastric cancer and recent progress of gastroendoscopic diagnosis and treatment for gastric cancer. *Jpn J Clin Oncol* 2010;40:828–37.
20. Shimizu N, Ikehara Y, Inada K, et al. Eradication diminishes enhancing effects of Helicobacter pylori infection on glandular stomach carcinogenesis in Mongolian gerbils. *Cancer Res* 2000;60:1512–4.
21. Nozaki K, Shimizu N, Ikehara Y, et al. Effect of early eradication on Helicobacter pylori-related gastric carcinogenesis in Mongolian gerbils. *Cancer Sci* 2003;94:235–9.
22. Take S, Mizuno M, Ishiki K. Baseline gastric mucosal atrophy is a risk factor associated with the development of gastric cancer after

Helicobacter pylori eradication therapy in patients with peptic ulcer diseases. *J Gastroenterol* 2007;42(Suppl 17):21–7.
23. Takenaka R, Okada H, Kato J, et al. Helicobacter pylori eradication reduced the incidence of gastric cancer, especially of the intestinal type. *Aliment Pharmacol Ther* 2007;25:805–12.
24. Ogura K, Hirata Y, Yanai A, et al. The effect of Helicobacter pylori eradication on reducing the incidence of gastric cancer. *J Clin Gastroenterol* 2008;42:279–83.
25. Yanaoka K, Oka M, Ohata H, Yanaoka K, Oka M, Ohata H. Eradication of Helicobacter pylori prevents cancer development in subjects with mild gastric atrophy identified by serum pepsinogen levels. *Int J Cancer* 2009;125:2697–703.
26. Mabe K, Takahashi M, Oizumi H, et al. Does Helicobacter pylori eradication therapy for peptic ulcer prevent gastric cancer? *World J Gastroenterol* 2009;15:4290–7.
27. Wu CY, Kuo KN, Wu MS, Chen YJ, Wang CB, Lin JT. Early Helicobacter pylori eradication decreases risk of gastric cancer in patients with peptic ulcer disease. *Gastroenterology* 2009;137:1641–8.
28. Wong BC, Lam SK, Wong WM, et al. China Gastric Cancer Study Group. Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. *JAMA* 2004;291:187–94.
29. Fuccio L, Zagari RM, Eusebi LH, et al. Meta-analysis: can Helicobacter pylori eradication treatment reduce the risk for gastric cancer? *Ann Intern Med* 2009;151:121–8.
30. Correa P, Fontham ET, Bravo JC, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-*Helicobacter pylori* therapy. *J Natl Cancer Inst* 2000;92:1881–8.
31. You WC, Brown LM, Zhang L, et al. Randomized double-blind factorial trial of three treatments to reduce the prevalence of precancerous gastric lesions. *J Natl Cancer Inst* 2006;98:974–83.
32. Saito D, Boku N, Fujioka T, Fukuda Y. Impact of *H. pylori* eradication on gastric cancer prevention: endoscopic results of the Japanese Intervention Trial (JITHP-Study). A randomized multi-center trial [Abstract]. *Gastroenterology* 2005;128:A4.
33. Zhou L. Ten-year follow-up study on the incidence of gastric cancer and the pathological changes of gastric mucosa after *H. pylori* eradication in China [Abstract]. *Gastroenterology* 2008;134:A233.
34. Ford AC, Moayyedi P. Redundant data in the meta-analysis on Helicobacter pylori eradication. *Ann Intern Med* 2009;151:513; author reply 513–4.
35. Maehata Y, Nakamura S, Fujisawa K, et al. Long-term effect of Helicobacter pylori eradication on the development of metachronous gastric cancer after endoscopic resection of early gastric cancer. *Gastrointest Endosc* 2012;75:39–46.
36. Kato M, Asaka M, Ono S, et al. Eradication of *Helicobacter pylori* for Primary Gastric Cancer and Secondary Gastric Cancer after EMR. *J Gastroenterol* 2007;42(Suppl 17):16–20.
37. Asaka M, Kato M, Graham DY. Prevention of gastric cancer by *Helicobacter pylori* eradication. *Intern Med* 2010;49:633–6.
38. Isobe Y, Nashimoto A, Akazawa K, et al. Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. *Gastric Cancer* 2011;14:301–16.
39. Hamashima C, Saito H, Nakayama T, Nakayama T, Sobue T. The standardized development method of the Japanese guidelines for cancer screening. *Jpn J Clin Oncol* 2008;38:288–95.
40. Hamashima C, Shibuya D, Yamazaki H, et al. The Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol* 2008;38:259–67.
41. Asaka M, Kato M, Graham DY. Strategy for eliminating gastric cancer in Japan. *Helicobacter* 2010;15:486–90.
42. Asaka M, Kato M, Takahashi S, et al. Japanese Society for Helicobacter Research. Guidelines for the management of Helicobacter pylori infection in Japan: 2009 revised edition. *Helicobacter* 2010;15:1–20.
43. Nakajima S, Nishiyama Y, Yamaoka M, Yasuoka T, Cho E. Changes in the prevalence of Helicobacter pylori infection and gastrointestinal diseases in the past 17 years. *J Gastroenterol Hepatol* 2010;25:S99–S110.
44. Hayashi Y, Yamamoto Y, Suganuma T, et al. Comparison of the diagnostic utility of the ultrathin endoscope and the conventional endoscope in early gastric cancer screening. *Dig Endosc* 2009;21:116–21.
45. Yagi J, Adachi K, Arima N, et al. A prospective randomized comparative study on the safety and tolerability of transnasal esophagogastroduodenoscopy. *Endoscopy* 2005;37:1226–31.
46. Murata A, Akahoshi K, Sumida Y, Yamamoto H, Nakamura K, Nawata H. Prospective randomized trial of transnasal versus peroral endoscopy using an ultrathin videoendoscope in unsedated patients. *J Gastroenterol Hepatol* 2007;22:482–5.
47. Tashiro A, Sano M, Kinameri K, Fujita K, Takeuchi Y. Comparing mass screening techniques for gastric cancer in Japan. *World J Gastroenterol* 2006;12:4873–4.
48. Matsumoto S, Yamasaki K, Tsuji K, Shirahama S. Results of mass endoscopic examination for gastric cancer in Kamigoto Hospital, Nagasaki Prefecture. *World J Gastroenterol* 2007;13:4316–20.
49. Samloff IM. Cellular localization of group I pepsinogens in human gastric mucosa by immunofluorescence. *Gastroenterology* 1971;61:185–8.
50. Samloff IM, Liebman WM. Cellular localization of the group II pepsinogens in human stomach and duodenum by immunofluorescence. *Gastroenterology* 1973;65:36–42.
51. Sipponen P, Samloff IM, Saukkonen M, Varis K. Serum pepsinogens I and II and gastric mucosal histology after partial gastrectomy. *Gut* 1985;26:1179–82.
52. Samloff IM, Stemmermann GN, Heilbrum LK, Nomura A. Elevated serum pepsinogen I and II levels differ as risk factors for duodenal ulcer and gastric ulcer. *Gastroenterology* 1986;90:570–6.
53. Miki K, Ichinose M, Shimizu A, et al. Serum pepsinogens as a screening test of extensive chronic gastritis. *Gastroentrol Jpn* 1987;22:133–41.
54. Borch K, Axelsson CK, Halgreen H, Damkjaer N, Ledin T, Szesci PB. The ratio of pepsinogen A to pepsinogen C: a sensitive test for atrophic gastritis. *Scand J Gastroenterol* 1989;24:870–6.
55. Asaka M, Kato M, Kudo M, et al. Relationship between Helicobacter pylori infection, atrophic gastritis and gastric carcinoma in a Japanese population. *Eur J Gastroenterol Hepatol* 1995;7(Suppl 1):S7–10.
56. Watabe H, Mitsushima T, Yamaji Y, et al. Predicting the development of gastric cancer from combining Helicobacter pylori antibodies and serum pepsinogen status: a prospective endoscopic cohort study. *Gut* 2005;54:764–8.
57. Oishi Y, Kiyohara Y, Kubo M, et al. The serum pepsinogen test as a predictor of gastric cancer: the Hisayama study. *Am J Epidemiol* 2006;163:629–37.
58. Yanaoka K, Oka M, Mukoubayashi C, et al. Cancer high-risk subjects identified by serum pepsinogen tests: outcomes after 10-year follow-up in asymptomatic middle-aged males. *Cancer Epidemiol Biomarkers Prev* 2008;17:838–45.
59. Yoshihara M, Hiyama T, Yoshida S, et al. Reduction in gastric cancer mortality by screening based on serum pepsinogen concentration: a case-control study. *Scand J Gastroenterol* 2007;42:760–4.
60. Ohata H, Kitauchi S, Yoshimura N, et al. Progression of chronic atrophic gastritis associated with Helicobacter pylori infection increases risk of gastric cancer. *Int J Cancer* 2004;109:138–43.
61. Mizuno S, Miki I, Ishida T, et al. Prescreening of a high-risk group for gastric cancer by serologically determined Helicobacter pylori infection and atrophic gastritis. *Dig Dis Sci* 2010;55:3132–7.
62. Miki K. Gastric cancer screening by combined assay for serum anti-Helicobacter pylori IgG antibody and serum pepsinogen levels—'ABC method'. *Proc Jpn Acad Ser B Phys Biol Sci* 2011;87:405–14.
63. Fock KM, Talley N, Moayyedi P, et al. Asia-Pacific consensus guidelines on gastric cancer prevention. *J Gastroenterol Hepatol* 2008;23:351–65.
64. Fock KM, Katelaris P, Sugano K, et al. Second Asia-Pacific Consensus Guidelines for Helicobacter pylori infection. *J Gastroenterol Hepatol* 2009;24:1587–600.
65. Koinuma N, Ogata T, Misawa J. Pharmacoeconomic assessment of gastric cancer treatment (In Japanese). *Nippon Rinsho* 2008;66:639–52.
66. Asaka M. Extermination of gastric cancer from Japan (In Japanese). *Nippon Shokakibyo Gakkai Zasshi* 2010;107:359–64.

Digestive Endoscopy 2013; **25**: 264–273 doi: 10.1111/j.1443-1661.2012.01385.x

Original Article

Changes in endoscopic findings of gastritis after cure of *H. pylori* infection: Multicenter prospective trial

Mototsugu Kato,[1] Shuichi Terao,[2] Kyoichi Adachi,[3] Shigemi Nakajima,[4] Takashi Ando,[5] Norimasa Yoshida,[6] Noriya Uedo,[7] Kazunari Murakami,[8] Shuichi Ohara,[9] Masanori Ito,[10] Naomi Uemura,[11] Takuro Shimbo,[12] Hidenobu Watanabe,[13] Takahiro Kato,[14] Kazunori Ida[14] and The Study Group for Establishing Endoscopic Diagnosis of Chronic Gastritis*

[1]Division of Endoscopy, Hokkaido University Hospital, Sapporo, [2]Department of Gastroenterology, Kakogawa West City Hospital, Hyogo, [3]Department of Clinical Nursing, Shimane University Faculty of Medicine, Shimane, [4]Department of Medicine, Gastroenterology and Health-care, Social Insurance Shiga Hospital, Shiga, [5]Department of Gastroenterology, Social Insurance Kyoto Hospital and [6]Department of Gastroenterology, Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, [7]Department of Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, [8]Department of General Medicine, Faculty of Medicine, Oita University, Oita, [9]Department of Gastroenterology, Tohoku Rosai Hospital, Sendai, [10]Department of Medicine and Molecular Science, Hiroshima University, Hiroshima, [11]Department of Gastroenterology, Kohnodai Hospital, National Center for Global Health and Medicine and [12]Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo, [13]Department of Pathology, Niigata University, Niigata, and [14]Department of Internal Medicine, Asahi University Murakami Memorial Hospital, Gifu, Japan

Background and Aim: Successful eradication of *H. pylori* changes pathological findings of gastritis dramatically. However, change of endoscopic mucosal findings is not fully understood. To clarify the short-term changes of endoscopic mucosal findings after cure of *H. pylori* infection, a multicenter prospective trial was conducted.

Methods: One hundred and forty-seven patients with *H. pylori* infection from 12 institutions were enrolled into this prospective cohort trial. Nineteen endoscopic findings using high-resolution white light electronic endoscopy were assessed before and 2–4 months after eradication treatment of *H. pylori*. *H. pylori* infection was diagnosed by pathology of three stomach sites using hematoxylin-eosin stain or *H. pylori*-specific immunostaining. Endoscopic features of the successful eradication group and the failed eradication group were compared. The change of severity of endoscopic features before and after *H. pylori* eradication were compared between successful eradication and failed eradication.

Results: One hundred and twenty-six patients were analyzed. Eradication rate was 81% (102/126). Non-transparency of gastric juice, diffuse redness of fundic mucosa, enlarged fold, spotty redness of fundic mucosa, flat erosion of stomach, and hemoglobin index of fundic mucosa were significantly different between the successful eradication group and the failed eradication group. Gastric flat erosion was of higher frequency in the successful eradication group. When eradication was successful, spotty redness of fundic gland improved significantly.

Conclusion: Assessment of endoscopic findings of spotty redness after eradication treatment is useful in the diagnosis of *H. pylori* eradication.

Key words: chronic gastritis, diffuse redness, endoscopic findings, erythema, *H. pylori* eradication

Corresponding: *Mototsugu Kato, Division of Endoscopy, Hokkaido University Hospital, North 14, West 5, Kita-ku, Sapporo, Hokkaido 060-8468, Japan. Email: m-kato@med.hokudai.ac.jp*

*The Study Group for Establishing Endoscopic Diagnosis of Chronic Gastritis

President: Kazunori Ida (Gifu).

Managers: Mototsugu Kato (Sapporo), Takahiro Kato (Gifu), Sachiyo Nomura (Tokyo), Shuichi Ohara (Sendai), Nobuhiro Sakaki (Tokyo), Takuro Shimbo (Tokyo), Noriya Uedo (Osaka), Naomi Uemura (Tokyo), Hidenobu Watanabe (Niigata).

Advisors: Michio Kaminishi (Tokyo), Kazumasa Miki (Tokyo), Saburou Nakazawa (Nagoya), Hirohumi Niwa (Tokyo), Masaharu Tatsuta(Osaka).

Contributors: Kyoichi Adachi (Shimane), Masanori Ito (Hiroshima), Mitsuru Kaise (Tokyo), Tomoari Kamada (Kurashiki), Takashi Kawai (Tokyo), Junichi Kawashima (Saitama), Atsushi Mitsunaga (Tokyo), Kazunari Murakami (Oita), Shigemi Nakajima (Otsu), Hiroyoshi Ota (Matsumoto), Shuichi Terao (Kakogawa), Takao Wakabayashi (Nagoya), Kazuyoshi Yagi (Niigata), Nobuaki Yagi (Kyoto), Norimasa Yoshida (Kyoto).

Received 5 May 2012; accepted 20 August 2012.

INTRODUCTION

HELICOBACTER PYLORI INFECTS the human stomach for life and causes chronic inflammation of the gastric mucosa.[1] *H. pylori* infection induces infiltration of mononuclear cells and polynuclear cells into the gastric mucosa.[2] Atrophic change and intestinal metaplasia often occur during long-term persistent infection. *H. pylori* infection leads to a wide variety of upper gastrointestinal tract diseases, such as gastroduodenal ulcer, gastric adenocarcinoma, gastric mucosal-associated lymphoid tissue lymphoma, and gastric hyperplastic polyps.[3–7] Successful eradication of *H. pylori* improves histological gastritis and may prevent various diseases associated with *H. pylori* infection.[8]

It has long been believed that the features of conventional white light endoscopy correlate poorly with histopathological findings of *H. pylori*-induced gastritis.[9,10] Regular arrangement of collecting venules (RAC) was reported to be an endoscopic feature with high sensitivity and high specificity for the *H. pylori*-negative normal stomach.[11] Studies using magnifying endoscopy have shown that endoscopic features are associated with histopathological findings related to *H. pylori* infection.[12–14] Successful eradication of *H. pylori* dramatically changes the histopathological findings of gastritis. Recently, changes of magnifying endoscopic features with narrow band imaging (NBI) were investigated during *H. pylori* eradication.[15,16] However, change of conventional white light endoscopic features have not been clarified. A multicenter prospective trial was conducted to elucidate short-term changes of conventional white light endoscopic features after cure of *H. pylori* infection.

METHODS

Subjects

THIS MULTICENTER PROSPECTIVE trial comprised 12 institutions affiliated with the 'Study group for establishing endoscopic diagnosis of chronic gastritis' founded by the Japan Gastroenterological Endoscopy Society. This study group conducted other studies on the relationship between findings of white light endoscopy and histological findings. One hundred and forty-seven patients with *H. pylori* infection were initially enrolled from January 2009 to December 2009. Patients eligible for enrollment aged 20 years or older received eradication treatment of *H. pylori* infection. Exclusion criteria were histories of gastric surgery, gastrectomy, and eradication of *H. pylori*, treatment with non-steroidal anti-inflammatory drugs, antiplatelet agents, anticoagulants, steroids, antibiotics, and proton pump inhibitors within 4 weeks prior to entry, severe liver, renal, and cardiopulmonary dysfunctions, blood diseases including anemia, and a hemorrhagic tendency.

This study was approved by the Ethics Committee of each institution and carried out in conformity with the Declaration of Helsinki. All subjects gave written informed consent.

Procedures

Enrolled patients received high-resolution white light endoscopic examination to assess endoscopic findings before *H. pylori* eradication. *H. pylori* infection was diagnosed by rapid urease test upon initial endoscopic examination or by ^{13}C urea breath test prior to study. After the initial endoscopy, 10 mg rabeprazole, 200 mg clarithromycin, and 750 mg amoxicillin were given twice a day for 1 week, according to Japanese guidelines for management of *H. pylori* infection.[17] In patients with active gastric and duodenal ulcer disease, a proton pump inhibitor or a histamine receptor antagonist was given for 5 to 7 weeks after eradication therapy. A second endoscopic examination was carried out 2–4 months after eradication treatment and at least 4 weeks after completion of proton pump inhibitor treatment. Results of *H. pylori* eradication were diagnosed by pathological examination of three stomach sites during the second endoscopy. Diagnostic tools in which the result is known within a short time, such as the urea breath test, were excluded from this study in order to keep the endoscopist blinded to the eradication result. Biopsy samples were taken from one site each in the greater curvature of the antrum, the greater curvature of the upper body, and the lesser curvature of the angle. One specialized pathologist (H.W.) carried out blind assessment of *H. pylori* infection using hematoxylin-eosin (HE) staining or *H. pylori*-specific immunostaining. As immunostaining was added for distinguishing *H. pylori* from other microorganisms and also for detecting coccoid forms of *H. pylori*, the accuracy of histological diagnosis was expected to be the same as that of the urea breath test. Comparisons were made of the endoscopic features of successful and failed eradication groups and of the endoscopic features before and after successful eradication. End point was the diagnostic characteristics of endoscopic findings after successful eradication of *H. pylori*.

Endoscopic assessment

All endoscopists involved in the present study were accredited members of the Japan Gastroenterological Endoscopy Society. The high-resolution white light endoscope in this study was the GIF-240 series or the GIF-260 series (Olympus Medical Systems, Tokyo, Japan). Chromoendoscopy using 0.2% indigocarmine was carried out after the completion of conventional observation of the target region. Hemoglobin (Hb) index values of the fundic mucosa were carried out by institutions familiar with this method. Hb index

was measured using an image-processing system according to a previous report.[18] Two close-up pictures of the fundic mucosa without specific lesions, such as erosion and patchy redness, were obtained at the posterior wall of the upper gastric body. Characteristics of 10 endoscopic features were defined mainly based on endoscopic division of the Sydney System.[19] Another nine features, such as non-transparency of gastric juice, diffuse redness, RAC, adhesive mucus, xanthoma, fundic gland polyp, extent of atrophy, swelling of pyloric gland region with indigocarmine staining, and Hb index of fundic mucosa, were added to evaluate the endoscopic findings. The 19 features are described below.

1 Non-transparency of gastric juice: This is determined by visibility of gastric mucosa at the bottom of gastric juice. Severity increases as visibility decreases.
2 Diffuse redness of fundic mucosa: This refers to uniform redness involving the entire mucosa of the fundic gland. RAC is visible without diffuse redness.
3 Mucosal edema (fundic/pyloric mucosa): This is characterized by soft, thick, and swollen gastric mucosa.
4 Enlarged fold: This constitutes fold enlargement. Normal fold is straight, smooth, and approximately 5 mm in diameter.
5 Visibility of vascular pattern: Atrophy is diagnosed by the visibility of the vascular pattern and rugal atrophy.
6 RAC: Starfish-like red spots in a regular arrangement are visible through the mucosal surface in the fundic gland region. Visibility of RAC is affected by inflammation and atrophy[11]
7 Nodularity: Nodular protrusions measuring 2–3 mm are uniformly distributed in the antrum and angle. Severities of the qualitative findings from categories 1 to 7 listed above were divided into four grades: none (–), intermediate (+/–), clear (+), and remarkable (2+) (Fig. 1).
8 Adhesive mucus: Grayish or yellowish mucus adheres to the mucosal surface prior to washing with water.
9 Spotty redness of fundic mucosa: Multiple tiny reddish spots are observed in the fundic gland region. This finding should be strictly differentiated from patchy redness in the point of location, size and number. Typical spotty redness is defined as tiny reddish lesions <1 mm in diameter that occur infinitely on the cardiac side of the fundic gland region.
10 Patchy redness (stomach/duodenum): It is defined as localized reddish macula of various sizes. It occurs once or frequently, but it is isolated.
11 Red streaking: It is defined as reddish longitudinal streaks in the antrum and corpus.
12 Flat erosion (stomach/duodenum): It is characterized by mucosal defects and whitish patches that vary in size.
13 Raised erosion: It is characterized as elevated mucosa with white excavation at the center.
14 Bleeding spot: It is defined as punctuated or ecchymotic reddish or brown- blackish flecks present in the gastric wall.
15 Xanthoma: It is characterized as yellow-white, well-demarcated, single or multiple nodules or plaques that vary in size.
16 Fundic gland polyp: It is characterized as tiny, numerous and sessile, usually scattered in the fundic gland region. They have the same color as the gastric mucosa. Severities of the quantitative findings from categories 8 to 16 listed above were divided into four grades: 0 (–), 1 (+/–), 2–9 (+), and >10 (2+) (Fig. 2).
17 Extent of atrophy: The extent of atrophy was recorded according to the classification of Kimura and Takemoto.[20]
18 Swelling of areae gastricae in the pyloric gland region with indigocarmine staining: In the swollen areae gastricae, the inter-area groove is narrow. The classification was recorded according to Ida's paper.[21]
19 Hb index of fundic mucosa: Hb index is used as a parameter of the mucosal hemoglobin concentration and mucosal blood flow.[18] Calculated Hb index correlates value with the intensity of diffuse mucosal redness.

Statistical analysis

Statistical calculations were carried out with STATA ver. 11 software (StataCorp LP, College Station, TX, USA). The characteristics of eradicated subjects and failed subjects were compared by Wilcoxon signed-rank test, chi-squared test, or Student's *t*-test. Mann–Whitney rank-sum test or Student's *t*-test was used to assess the difference of endoscopic findings between the eradicated group and the failed group. Comparison of endoscopic findings before and after eradication in the two groups was analyzed using Wilcoxon signed-rank test. *P*-values <0.05 were considered to indicate statistical significance.

RESULTS

H. pylori eradication

ONE HUNDRED AND forty-seven patients with *H. pylori* infection were enrolled in the present study (Fig. 3). Seventeen patients were lost at the second endoscopic examination. Four patients were excluded for lack of histological specimens. Of the 126 patients in the final analysis, there were 69 with chronic gastritis, 20 with gastric ulcer scar, 12 with duodenal ulcer scar, 11 with active gastric ulcer, one with active duodenal ulcer, four after endoscopic resection of early gastric cancer, three with hyperplastic polyp, and six with miscellaneous diseases. The male-to-female ratio and mean age were 1.3 and 61.7 years, respec-

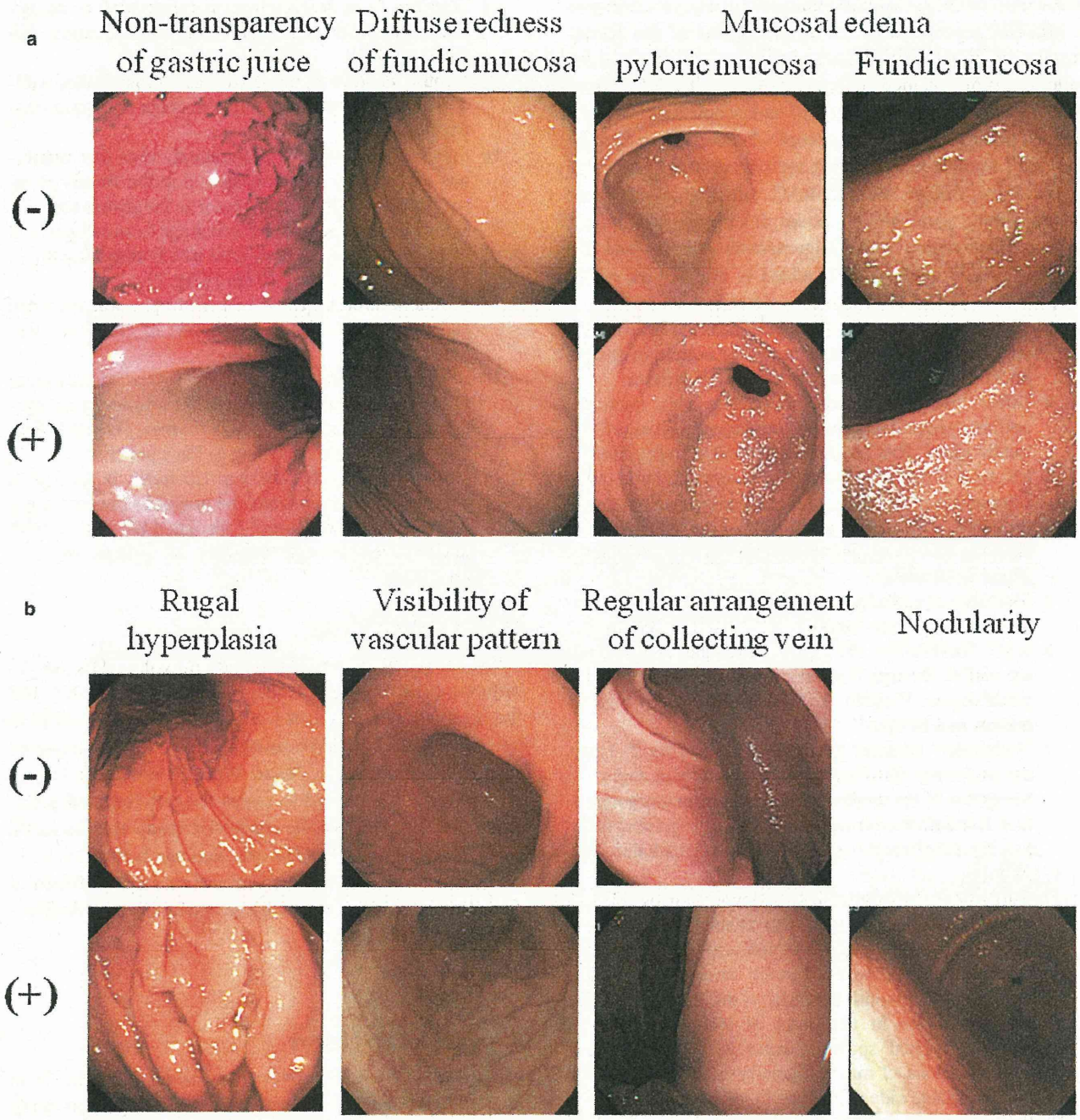

Figure 1 Grading of clear (+) and none (–) in the severity of seven qualitative findings.

tively. After eradication therapy of *H. pylori*, 102 patients were diagnosed with negative *H. pylori* infection using pathological examination and 24 patients were diagnosed with persistent *H. pylori* infection. Final eradication rate was 81% (102/126).

Comparison between successful and failed eradication group

Significant differences between the successful and failed eradication group were not seen in background characteris-

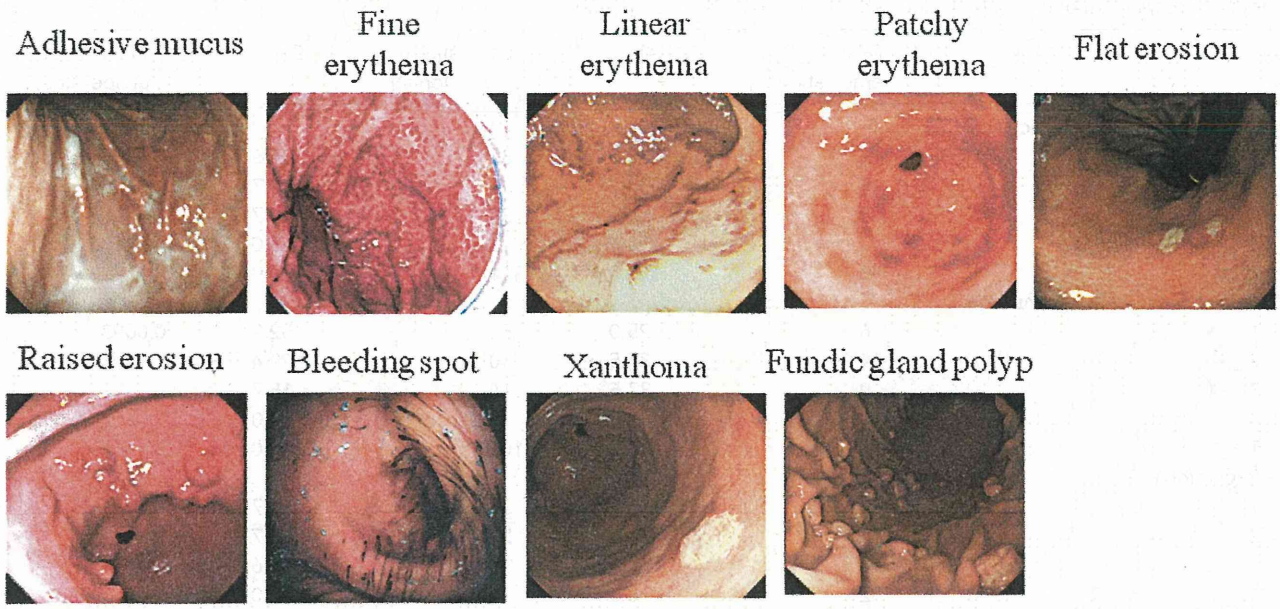

Figure 2 Nine quantitative findings.

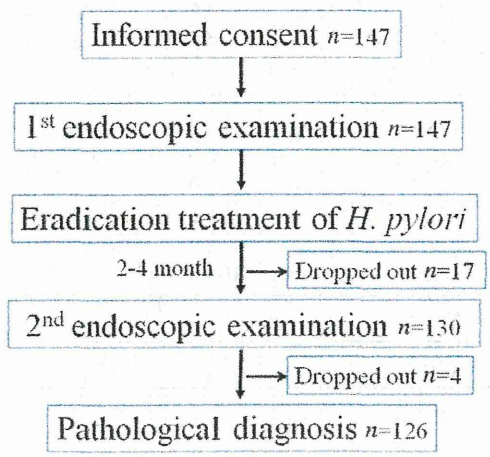

Figure 3 Protocol design.

tics such as age, sex, disease, and endoscopic findings, except diffuse redness of fundic mucosa. The successful eradication group had a lower grading in diffuse redness of the fundic mucosa than the failed group ($P = 0.0014$). Non-transparency of gastric juice, diffuse redness of fundic mucosa, enlarged fold, spotty redness of fundic mucosa, flat erosion of stomach, and Hb index of fundic mucosa after eradication were significantly different between the successful eradication group and the failed eradication group (Table 1). Other endoscopic findings had no significant differences (data not shown). Grading of endoscopic findings including diffuse redness, spotty redness, non-transparency of gastric juice, and enlarged fold were lower in the successful eradication group. Mean value of Hb index in the successful eradication group was lower than that in the failed eradication group. However, grading of gastric flat erosion was higher in frequency in the successful eradication group.

Comparison of change before and after *H. pylori* eradication between successful eradication and failed eradication

To evaluate specific endoscopic findings related to successful eradication and not to failed eradication, change of severity of endoscopic findings before and after *H. pylori* eradication were compared between successful eradication and failed eradication. Spotty redness of fundic mucosa was improved significantly in successful eradication cases compared with a small change in failed eradication cases (Table 2). Other significant endoscopic findings between the successful and failed eradication groups, in particular non-transparency of gastric juice, diffuse redness of fundic mucosa, enlarged fold, flat erosion of the stomach, and Hb index of fundic mucosa, did not show a significant difference because of an improvement in failed eradication cases (Table 3).

DISCUSSION

HELICOBACTER PYLORI INFECTION leads to various upper gastrointestinal tract diseases and influences gastric function, including gastric acid secretion. Successful

Table 1 Comparison between the failed and successful eradication groups

	Failed eradication (*n*)	(%)	Successful eradication (*n*)	(%)	*P* (rank-sum test if unspecified)
Non-transparency of gastric juice					
1	3	13.0	37	36.6	0.026
2	9	39.2	31	30.7	
3	8	34.8	30	29.7	
4	3	13.0	3	3.0	
Total	23	100.0	101	100.0	
Diffuse redness of fundic mucosa					
1	6	25.0	54	52.9	0.0093
2	9	37.5	30	29.4	
3	9	37.5	16	15.7	
4	0	0.0	2	2.0	
Total	24	100.0	102	100.0	
Enlarged fold					
1	4	16.7	31	30.7	0.038
2	5	20.8	29	28.7	
3	13	54.2	39	38.6	
4	2	8.3	2	2.0	
Total	24	100.0	101	100.0	
Spotty redness of fundic mucosa					
1	10	41.7	59	57.8	0.020
2	1	4.2	22	21.6	
3	11	45.8	19	18.6	
4	2	8.3	2	2.0	
Total	24	100.0	102	100.0	
Flat erosion of stomach					
1	22	91.7	72	70.5	0.035
2	0	0.0	2	2.0	
3	2	8.3	27	26.5	
4	0	0.0	1	1.0	
Total	24	100.0	102	100.0	
	Mean	SD	Mean	SD	
Hb index of fundic mucosa	62.4	4.6	57.8	5.7	0.030

Hb, hemoglobin.

Table 2 Change of spotty redness of fundic mucosa before and after *H. pylori* eradication between failed and successful eradication

	Failed eradication		Successful eradication		*P* (chi-squared test)
	(*n*)	(%)	(*n*)	(%)	
Spotty redness of fundic mucosa					
Non-improvement	19	79.2	56	54.9	0.029
Improvement	5	20.8	46	45.1	
Total	24	100.0	102	100.0	

eradication of *H. pylori* improves histological gastritis and may prevent various diseases associated with *H. pylori* infection, such as gastric/duodenal ulcer and gastric cancer.[22,23] Moreover, *H. pylori* eradication therapy is necessary to prevent the spread of this infection. The detection of *H. pylori* infection after eradication treatment is carried out using invasive and non-invasive tests such as pathological examination, culture, ^{13}C-urea breath test, and stool antigen test. The aim of

Table 3 Comparison of change before and after *H. pylori* eradication between failed and successful eradication

	Failed eradication		Successful eradication		*P* (chi-squared test or *Fisher's exact test)
	(*n*)	(%)	(*n*)	(%)	
Non-transparency of gastric juice					
Non-improvement	12	54.5	48	49.5	0.67
Improvement	10	45.5	49	50.5	
Total	22	100	97	100	
Diffuse redness of fundic mucosa					
Non-improvement	8	33.3	37	36.3	0.79
Improvement	16	66.7	65	63.7	
Total	24	100	102	100	
Mucosa edema of fundic mucosa					
Non-improvement	9	45.0	40	45.5	0.97
Improvement	11	55.0	48	54.5	
Total	20	100	88	100	
Mucosa edema of pyloric mucosa					
Non-improvement	8	40.0	36	42.4	0.85
Improvement	12	60.0	49	57.3	
Total	20	100	85	100	
Enlarged fold					
Non-improvement	16	66.67	48	48.98	0.12
Improvement	8	33.33	50	51.02	
Total	24	100	98	100	
Visibility of vascular pattern					
Non-improvement	19	79.2	81	79.4	0.98
Improvement	5	20.8	21	20.6	
Total	24	100	102	100	
Regular arrangement of collecting venules					
Non-improvement	23	95.8	90	89.1	0.46*
Improvement	1	4.2	11	10.9	
Total	24	100	101	100	
Nodularity					
Non-improvement	21	87.5	99	97.1	0.083*
Improvement	3	12.5	3	2.9	
Total	24	100	102	100	
Adhesive mucus					
Non-improvement	14	58.3	43	42.2	0.15
Improvement	10	41.7	59	57.8	
Total	24	100	102	100	
Patchy redness of stomach					
Non-improvement	20	83.3	79	77.5	0.53
Improvement	4	16.7	23	22.5	
Total	24	100	102	100	
Patchy redness of duodenum					
Non-improvement	23	95.8	94	94.0	1.00*
Improvement	1	4.2	6	6.0	
Total	24	100	100	100	
Red streaking					
Non-improvement	22	91.7	100	98.0	0.16*
Improvement	2	8.3	2	2.0	
Total	24	100	102	100	

Table 3 Comparison of change before and after *H. pylori* eradication between failed and successful eradication (*contintued*)

	Failed eradication		Successful eradication		*P* (chi-squared test or *Fisher's exact test)
	(*n*)	(%)	(*n*)	(%)	
Flat erosion of stomach					
Non-aggravation	22	91.67	95	93.14	0.68*
Aggravation	2	8.33	7	6.86	
Total	24	100	102	100	
Raised erosion					
Non-improvement	23	95.8	99	97.1	0.58*
Improvement	1	4.2	3	2.9	
Total	24	100	102	100	
Bleeding spot					
Non-improvement	22	91.7	95	93.1	0.35*
Improvement	2	8.3	7	6.9	
Total	24	100	102	100	
Xanthoma					
Non-improvement	24	100.0	95	93.1	0.35*
Improvement	0	0.0	7	6.9	
Total	24	100	102	100	
Fundic gland polyp					
Non-improvement	23	95.8	102	100.0	0.19*
Improvement	1	4.2	0	0	
Total	24	100	102	100	
Extent of atrophy					
Non-improvement	22	91.7	84	82.4	0.36*
Improvement	2	8.3	18	17.6	
Total	24	100	102	100	
Swelling of areae gastricae					
Non-improvement	15	83.3	63	78.7	1.00*
Improvement	3	16.7	17	21.3	
Total	18	100	80	100	
Hb index of fundic mucosa					
Non-improvement	2	25	12	36.36	0.692
Improvement	6	75	21	63.64	
Total	8	100	33	100	

Hb, hemoglobin.

the present study was to evaluate endoscopic diagnosis for successful eradication of *H. pylori* infection. Endoscopy can improve the accuracy of diagnosis of *H. pylori* infection during examination without the need for biopsy. In this study, various kinds of white light endoscopic features were assessed before and after *H. pylori* eradication. Almost of these features were described in an endoscopic division of the Sydney System.[19] Other findings such as non-transparency of gastric juice, diffuse redness, RAC, adhesive mucus, xanthoma, fundic gland polyp, extent of atrophy, swelling of pyloric gland region with indigocarmine staining, and Hb index of fundic mucosa were reported to be associated with *H. pylori* infection.[11–14]

From our results, a decrease in spotty redness after eradication treatment was a significantly useful endoscopic finding for the diagnosis of successful eradication. Comparison between the successful and failed eradication groups showed a significant difference in six endoscopic findings. However, five endoscopic findings such as diffuse redness of fundic mucosa, non-transparency of gastric juice, enlarged fold, flat erosion of stomach, and Hb index of fundic mucosa were not specific changes in cases of successful eradication. These endoscopic findings could possibly be associated with temporary inhibition of gastric inflammation by suppression of *H. pylori*. Spotty redness of the fundic gland region is strictly influenced by curing *H. pylori* infection. As the