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TOPIC HIGHLIGHT

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Endoscopic surveillance of gastric cancers after *Helicobacter pylori* eradication

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Abstract

The incidence and mortality of gastric cancer remains high in East Asian countries. Current data suggest that *Helicobacter pylori* (*H. pylori*) eradication might be more effective for preventing gastric cancer in young people before they develop atrophic gastritis and intestinal metaplasia. However, the long-term effect of *H. pylori* eradication on metachronous cancer prevention after endoscopic resection (ER) of early gastric cancer remains controversial, with some discordance between results published for Japanese and Korean studies. The detection ability of synchronous lesions before ER and eradication of *H. pylori* directly influences these results. After eradication, some gastric cancers are more difficult to diagnose by endoscopy because of morphologic changes that lead to a flat or depressed appearance. Narrow-band imaging with magnifying endoscopy (NBI-ME) is expected to be useful for identifying metachronous cancers. However, some gastric cancers after eradication show a "gastritis-like" appearance under NBI-ME. The gastritis-like appearance correlates with the histological surface differentiation of the cancer tubules and superficial non-neoplastic epithelium atop or interspersed with the cancer. Till date, it remains unclear whether *H. pylori* eradication could prevent progression of gastric cancer. Until we can establish more useful endoscopic examination methodologies, regular endoscopic surveillance of high-risk groups is expected to be the most beneficial approach for detection.

Key words: Gastric cancer; *Helicobacter pylori*; Atrophic gastritis; Narrow-band imaging; Magnifying endoscopy; Endoscopic resection

Core tip: Although *Helicobacter pylori* (*H. pylori*) eradication may prevent the development of gastric cancer, tumors can occur despite successful eradication. The characteristics and management of these cancers have therefore become major clinical issues. Because of indistinct borderline or surface structure, it is often difficult to diagnose gastric cancer using narrow-band imaging with magnifying endoscopy after eradication. We review the effect of *H. pylori* eradication on metachronous cancer prevention, endoscopic and histopathological findings of gastric cancers discovered after eradication, and discuss effective management strategies for early gastric cancer.

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INTRODUCTION

Despite declining incidence and mortality worldwide, gastric cancer is the third leading cause of cancer death, and continues to have a high mortality rate with nearly three-quarters of a million people dying annually[1]. Almost one million new cases of gastric cancer were estimated to have occurred in 2012, making it the fifth most common malignancy globally after cancers of the lung, breast, colorectum, and prostate. Of concern, China, Japan, and Korea, account for approximately 60% of all cases, with high incidences also present in Central and Eastern Europe, and in Central and South America.

The association between *Helicobacter pylori* (*H. pylori*) infection and the development of gastric cancer is well established by epidemiological[2] and experimental animal studies[3,4]. In 1994, the International Agency for Research on Cancer, a subsidiary of the World Health Organization, categorized *H. pylori* as a group 1 carcinogen for gastric cancer[5]. *H. pylori* infection is the most important risk factor for gastric adenocarcinoma, causing progressive damage to the gastric mucosa that may eventually result in atrophic gastritis and the subsequent intestinal metaplasia that is necessary for the development of gastric cancer[6]. It is now widely accepted that *H. pylori* infection accounts for more than 95% of gastric cancers, with the prevalence of strictly defined *H. pylori*-negative gastric cancer being extremely low in Japanese patients (0.42% or 0.66%)[7,8].

Recently, the use of *H. pylori* eradication therapy has spread worldwide[9,10], and in 2013, the Japanese health insurance system approved eradication therapy in patients with *H. pylori* gastritis. Although eradication is expected to help prevent the development of gastric cancer in these patients, cancers have sometimes been discovered after successful eradication. Along with the increasing use of *H. pylori* eradication therapy, the incidence of gastric cancer after *H. pylori* eradication has also been increasing.

This review therefore aims to outline effective management strategies for gastric cancer, focusing on East Asian countries where the incidence gastric cancer is still high. We review the effect of *H. pylori* eradication on metachronous cancer prevention and the endoscopic and histopathological findings of gastric cancers discovered after eradication, before discussing how gastric cancer can be detected at an early stage.

H. PYLORI ERADICATION FOR PRIMARY GASTRIC CANCER PREVENTION

The argument for *H. pylori* eradication as an effective means of gastric cancer prevention originated from epidemiological and interventional studies in animals[2-5]. In a clinical setting, Uemura *et al*[6] also reported that, in patients who were prospectively followed-up for a mean of 7.8 years, gastric cancers developed only in *H. pylori*-infected patients. In a subgroup analysis of their randomized controlled trial (7.5-year follow-up), Wong *et al*[11] reported that *H. pylori* eradication decreased the development of gastric cancer only in those without atrophic gastritis and intestinal metaplasia. Subsequently, a meta-analysis of six randomized controlled trials from China, Japan, and Colombia confirmed that successful eradication reduced the risk of gastric cancer. In the pooled analysis of 6695, largely Asian, participants followed for 4-10 years, the relative risk (RR) for gastric cancer following successful eradication therapy was just 0.65 (95%CI: 0.43-0.89)[12]. A recent Taiwanese study considered the role of mass eradication of *H. pylori* infection in the general population[13]. The authors compared the incidence of gastric cancer historically between approximately 5000 *H. pylori*-infected patients over 30 years old who received eradication therapy (2004-2008) with those who did not (1995-2003). They found significant effectiveness in reducing the incidence of gastric atrophy with chemoprevention (77.2%; 95%CI: 72.3%-81.2%), but found no significant reduction in intestinal metaplasia. The effectiveness of eradication therapy in reducing gastric cancer incidence was 25% (P = 0.21, RR = 0.753; 95%CI: 0.37-1.52). Further long-term follow-up study was therefore needed to verify whether meaningful reductions in the incidence of gastric cancer could be achieved.

The available data suggest that *H. pylori* eradication is an appropriate primary chemoprevention strategy in a subset of subjects. For example, *H. pylori* eradication might be more effective in preventing gastric cancer among younger people, before the development of atrophic gastritis and intestinal metaplasia. Indeed,

Table 1 Incidence of metachronous cancer after successful *Helicobacter pylori* eradication

Ref.	Country	Subject	Study design	Follow-up (yr)	Synchronous rate	Metachronous	Incidence (%)	Effect, OR (95%CI)
Uemura *et al*[15], 1997	Japan	65/67	NR	4	6 (9%)	> 0 yr	0.0/9.0	Effective, $P = 0.011$
Fukase *et al*[16], 2008	Japan	272/272	RCT	3	ND	> 0 yr	3.3/8.8	Effective, 0.35 (0.16-0.78) $P = 0.009$
Maehata *et al*[17], 2012	Japan	177/91	Retrospective	3 (1.1-11.1)	ND	> 1 yr	8.5/14.3	Non-effective, 1.71 (0.72-4.03)
Kato *et al*[18], 2013	Japan	263/105	Retrospective	2.2 (2-5)	110 (9%)	> 1 yr	9.1/5.7	Non-effective
Choi *et al*[19], 2013	South Korea	439/441	RCT	3 (2.0-4.5)	ND	> 0 yr	2.3/3.9	Non-effective, $P = 0.15$
Seo *et al*[20], 2013	South Korea	61/13	Retrospective	2.3	ND	> 1 yr	9.8/23.1	Non-effective, 0.36 (0.08-1.70) $P = 0.189$
Chon *et al*[21], 2013	South Korea	85/44	Retrospective	2.2 (1.4-2.5)	ND	> 1 yr	4.7/11.4	Effective, HR = 0.143, $P = 0.008$
Bae *et al*[22], 2014	South Korea	485/182	Retrospective	5 (2-11.4)	ND	> 6 mo	7.0/13.2	Effective, HR = 1.9, $P = 0.01$
Kwon *et al*[23], 2014	South Korea	214/69	Retrospective	3.4 (3-5)	ND	> 1 yr	4.7/14.5	Effective, 2.3 (1.1-4.7) $P = 0.021$
Kim *et al*[24], 2014	South Korea	49/107	Retrospective	4.3 (1-11.3)	5 (3%)	> 1 yr	4.1/15.0	Effective, $P = 0.006$
Jung *et al*[25], 2015	South Korea	506/169	Retrospective	3.3	15%	> 1 yr	4.2/5.9	Non-effective, HR = 0.67, $P = 0.29$

Number of subjects with/without eradication. NR: Non-randomized; RCT: Randomized controlled trial; Follow-up: Median (range); ND: Not described; Metachronous: Metachronous cancer classified as a second lesion within 1 year (> 0 year) or after 1 year (> 1 year); Incidence: Percentage of metachronous lesions with/without eradication including failure; OR: Odds ratio; CI: Confidence interval; HR: Hazard ratio.

the Japanese health insurance system expanded the application of medical insurance for *H. pylori* eradication to all patients with chronic gastritis. However, *H. pylori* eradication in patients who have already developed advanced pre-neoplastic lesions is probably unable to prevent gastric cancer development completely.

H. PYLORI ERADICATION FOR METACHRONOUS CANCER PREVENTION

Current guidelines recommend *H. pylori* eradication after endoscopic resection (ER) of early gastric cancer to prevent or reduce the development of metachronous gastric cancer[10,14]. However, the long-term effect of *H. pylori* eradication on the prevention of metachronous cancer after ER remains controversial.

Uemura *et al*[15] first reported in an observational study that *H. pylori* eradication after ER reduced the occurrence of new gastric cancer. Thereafter, Fukase *et al*[16] conducted a multi-center, open-label, randomized controlled trial among *H. pylori*-positive gastric cancer patients who underwent ER. They reported that the odds ratio (OR) for metachronous gastric cancer was 0.35 (95%CI: 0.16-0.78; $P = 0.009$) for the group receiving *H. pylori* eradication therapy compared with the control group. This served as the basis for recommending *H. pylori* eradication after ER in Japan. However, two subsequent retrospective studies in Japan have shown that, during long-term follow-up, *H. pylori* eradication does not reduce the incidence of metachronous gastric cancer in patients who underwent ER for early gastric cancer. Although Maehata *et al*[17] reported that *H. pylori* eradication seemed to reduce the incidence of metachronous gastric cancer at the 5-year follow-up point, the effect disappeared after 5 years of follow-up. In addition, Kato *et al*[18] reported that *H. pylori* eradication did not reduce the development of metachronous gastric cancer throughout the follow-up period[19].

A recent Korean open-label prospective study reported that *H. pylori* eradication after ER did not reduce the incidence of metachronous gastric cancer[19]. During a median follow-up period of 3 years in 901 patients, 10 patients who received *H. pylori* eradication and 17 controls developed metachronous cancer ($P = 0.15$). Many other retrospective studies from Korea have also reported different outcomes from *H. pylori* eradication after ER with respect to the incidence of metachronous gastric cancer[20-25].

An important issue is therefore why the studies from Japan and Korea should report such different results. The reason might be related to differences in study design; for example, Table 1 summarizes the studies into the incidence of metachronous cancer after successful *H. pylori* eradication together with their study designs. Indeed, several points contributed to the study results.

First, the definitions of metachronous cancer that were used were not consistent. The study by Fukase *et al*[16] considered lesions detected within 1 year after ER as metachronous cancer, while most of other studies excluded patients who had a new lesion within 1 year. Indeed, the latter approach is probably ideal because the development of secondary lesions within 1 year generally implies that a synchronous lesion was overlooked during the initial procedure. Nevertheless, this issue makes it difficult to compare these study results directly. For example, Figure 1 shows a Kaplan-Meier analysis of the data for our institute[26]. When

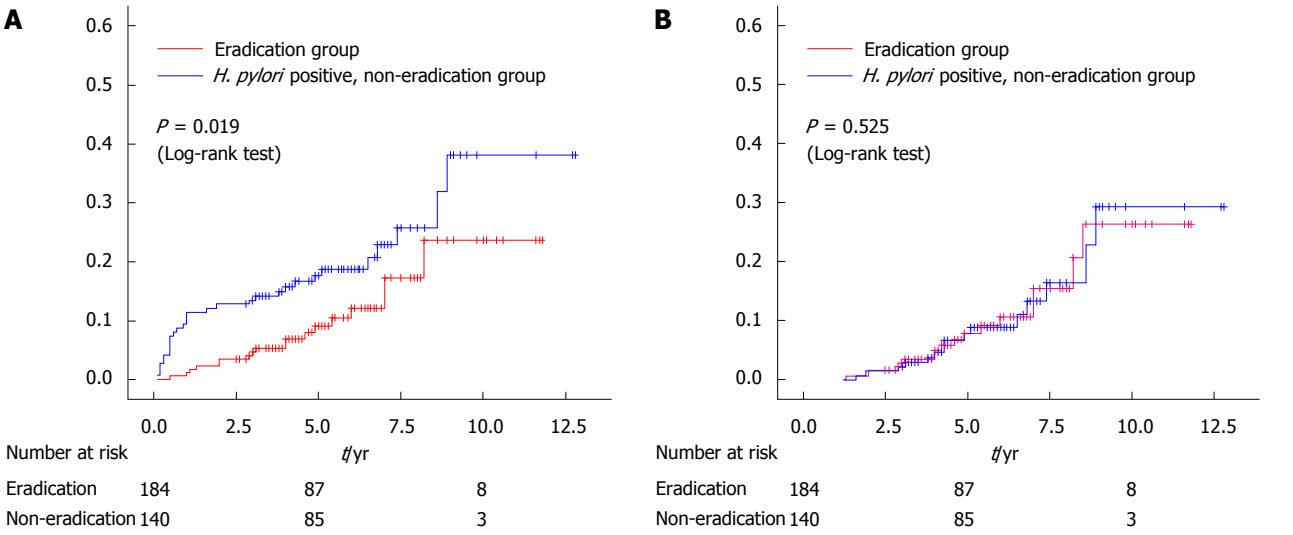

Figure 1 Kaplan-Meier analysis of the cumulative incidence rate of metachronous cancer in patients with and without *Helicobacter pylori* eradication therapy after endoscopic resection of early gastric cancer (adapted from our institute data[26]). A: When second lesions detected within 1 year after endoscopic resection (ER) were handled as metachronous cancers, the detection rate in the eradication group was reduced significantly ($P = 0.019$, Log-rank test) compared with the non-eradication group; B: In contrast, when second lesions were defined as overlooked synchronous cancers and excluded from the metachronous cancer group, there was no significant difference between the two groups.

second lesions detected within 1 year after ER were handled as metachronous cancer, the detection rate in the eradication group was reduced significantly compared with that of the persistent *H. pylori* infection group. However, when these second lesions were excluded as synchronous cancers, there was no difference between the two groups. Although the overlooked synchronous lesions would usually be detected 1-2 years after ER, the study of Fukase *et al*[16] revealed that metachronous lesions were detected 6-12 mo only in the non-eradication group, with no overlooked second lesions in the eradication group. These differences may be due to the effect of eradication therapy on the endoscopic appearance of second lesions. That is, *H. pylori* eradication therapy can make endoscopic diagnosis difficult by leaving an indistinct border and can obscure cancerous appearances. If eradication therapy influences tumor morphology, this may affect the tumor discovery rate. At present, researchers can only evaluate the discovery rate of gastric cancer by endoscopic examination, and not the true occurrence.

Second, the timing of *H. pylori* eradication therapy might influence the results between two randomized studies. The study of Choi *et al*[19] used a scheduled eradication therapy within 2 wk after ER. In contrast, Fukase *et al*[16] formed two groups, as follows: a newly diagnosed group that received immediate eradication therapy after ER, including those with a secondary lesion detected within 1 year; and a post-ER group that was followed for several years before receiving eradication therapy, excluding those who developed another gastric cancer before entry. In the subgroup analysis, the authors confirmed that the eradication effect was only seen in the post-ER group (RR = 0.27; 95%CI: 0.09-0.79) and not in the newly diagnosed group (RR = 0.46; 95%CI: 0.16-1.33). Due to the comparable study design, the data for the newly diagnosed group were comparable to those of Choi *et al*[19]. Therefore, the analysis by Fukase *et al*[16] suggests that eradication was effective in patients with a single cancer lesion after excluding those with multiple lesions. If patients with multiple cancers have more severe risk factors, such as severe mucosal atrophy or intestinal metaplasia, it is reasonable to assume that the effect of eradication would be limited to patients with relatively low risk.

Third, the accuracy of endoscopic examination has a direct influence on the study results. For example, the incidence of synchronous lesions discovered before ER can be used to evaluate the accuracy of endoscopic examination, with some synchronous lesions potentially being overlooked and detected after 1 year or later during surveillance endoscopy. If the incidence of synchronous lesions is low, then second lesions can more frequently be detected as a metachronous cancer in the follow-up study. It is therefore unfortunate that the incidences of synchronous lesions discovered at the initial ER were not described in most of the previous reports (Table 1). Gastric cancer generally has a long natural course[27], with a relatively long doubling time of 1.6-9.5[28] or 1.4 years[29]. Therefore, if a synchronous lesion was slow-growing and overlooked during the initial procedure, it is possible that the lesion could be discovered over 5 years later. There are many reports about synchronous multiple gastric cancers among the patients treated by ER, with an incidence ranging from 2.0% to 19.2%[15,18,30-37]

Table 2 Incidence of multiple gastric cancers after endoscopic resection of primary early gastric cancer *n* (%)

Ref.	Country	Subject	Follow-up (yr)	Synchronous cancers	Metachronous cancers
Arima *et al*[30], 1999	Japan	76	7	5 (6.6)	6 (7.9)
Nasu *et al*[31], 2005	Japan	143	13.1 (median 4.8)	16 (11.2)	20 (14.0)
Nakajima *et al*[32], 2006	Japan	633	13.9 (mean 4.4)	58 (9.2)	53 (8.2)
Kobayashi *et al*[33], 2010	Japan	234	19.6 (median 5.0)	45 (19.2)	30 (12.8)
Han *et al*[34], 2011	South Korea	176	4	7 (4.0)	9 (5.1)
Kato *et al*[18], 2013	Japan	1258	6 (mean 2.2)	110 (8.7)	65 (5.2)
Kim *et al*[35], 2013	South Korea	602	ND	12 (2.0)	ND
Boda *et al*[36], 2014	Japan	357	9.5 (median 4.4)	50 (14.0)	39 (10.9)
Kosaka *et al*[37], 2014	Japan	438	9.8	45 (10.2)	34 (7.8)

Number of subjects without eradication. ND: Not described; Synchronous cancers: Second gastric cancers discovered within 1 yr after the initial endoscopic resection; Metachronous cancers: Second gastric cancers discovered 1 yr or later from the initial endoscopic resection.

(Table 2). In these reports, there is a consensus that cancers detected within 1 year after the initial ER should be regarded as "missed" synchronous cancers. Our rate of synchronous cancers was highest (19.2%) in the previous studies. In addition, we reviewed pre-ER pictures, which detected 22.2% (8/36) of metachronous (*i.e.*, missed synchronous) cancers. Therefore, the accurate detection rate of synchronous cancer was more than 20% at our institution[33], although Niigata is a prefecture with a particularly high level of gastric cancer mortality[38].

Fourth, the study results depend on the follow-up time of endoscopic surveillance. In a multivariate logistic regression analysis, Maehata *et al*[17] reported that a follow-up time longer than 5 years was an independent risk factor for metachronous gastric cancer. Considering the relatively long doubling time of early gastric cancer[27-29], follow-up times longer than 5 years are needed for reliable study. To date, short follow-up studies seem to reveal that *H. pylori* eradication inhibits the growth of existing gastric cancer rather than inhibiting new occurrences. We should be aware of this influence of eradication on the endoscopic detection of gastric cancer.

A recent systematic meta-analysis demonstrated the beneficial effects of *H. pylori* eradication. Using the data from 13 trials and 3 prospective trials, the ORs were 0.42 (95%CI: 0.32-0.56) in the eradication group when compared with the control group[39]. Therefore, *H. pylori* eradication therapy should be recommended for patients who have undergone ER of gastric cancers. However, regular surveillance endoscopy is also recommended for the early detection of common metachronous cancers.

ENDOSCOPIC FINDINGS OF GASTRIC CANCERS AFTER *H. PYLORI* ERADICATION

Gastric cancers detected after eradication are typically reported to be small in size, to have less cell proliferation, to have flat or depressed-type macroscopic features, and to have a gastric or gastric-predominant mucin phenotype[40-42]. Because most of these lesions were detected in regular surveillance endoscopy, they might be expected to be small and to have a lower grade of histological atypia and cell proliferation. Together with Ito *et al*[43], we previously investigated the morphological changes in gastric cancer following *H. pylori* eradication[44] reporting that after a short follow-up period, some of the tumors developed a depressed appearance. A recent report concerning the morphologic changes in gastric adenomas after eradication also revealed that 12 lesions (44%) showed macroscopic and histologic regression at an average of 19.9 mo after eradication therapy[45]. These depressed-type macroscopic features were relatively difficult to discern through ordinary endoscopic observation. Even if the true occurrence of new cancer remained unaffected, the clinical incidence of metachronous cancer or adenoma would be influenced by the eradication effect. A representative case of gastric cancer that developed flat-type macroscopic features after eradication therapy is shown in Figure 2[46].

MAGNIFYING NARROW-BAND IMAGING OF EARLY GASTRIC CANCERS AFTER *H. PYLORI* ERADICATION

Narrow-band imaging with magnifying endoscopy (NBI-ME), a recently developed advanced endoscopic imaging technology, is recommended for the accurate diagnosis of gastric cancer. NBI-ME and other image-enhanced endoscopy techniques are thought to be useful when inspecting minute or occult metachronous gastric cancer. However, a potential pitfall is that NBI-ME may not be useful for the early detection of gastric cancers after *H. pylori* eradication therapy. We should therefore understand the endoscopic and histopathological characteristics of theses lesions.

In a previous report by Ito *et al*[43], non-neoplastic epithelium covered the cancerous tissue after eradication. In addition, using Ki-67 immunohisto-chemistry, we have demonstrated surface differentiation in approximately 40% of gastric cancers after

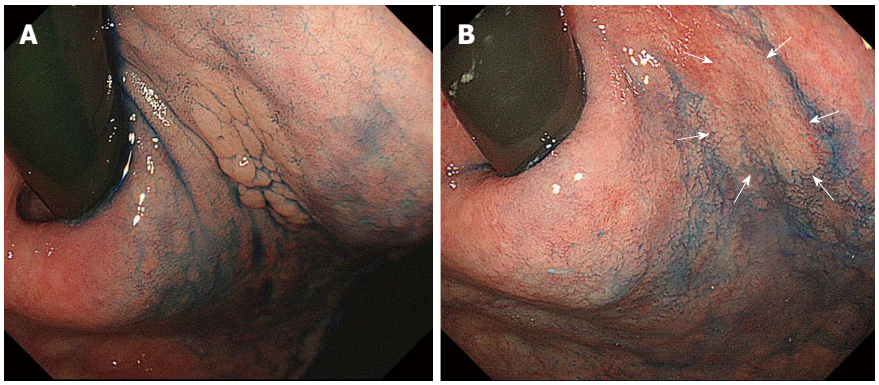

Figure 2 Gastric adenoma detected before 4 years with a granular appearance (A) and this lesion became flat and the granules disappeared after successful *Helicobacter pylori* eradication therpy (B). It was difficult to identify the border (arrows) by chromoendoscopy. After endoscopic submucosal dissection, the histological diagnosis was adenocarcinoma[46].

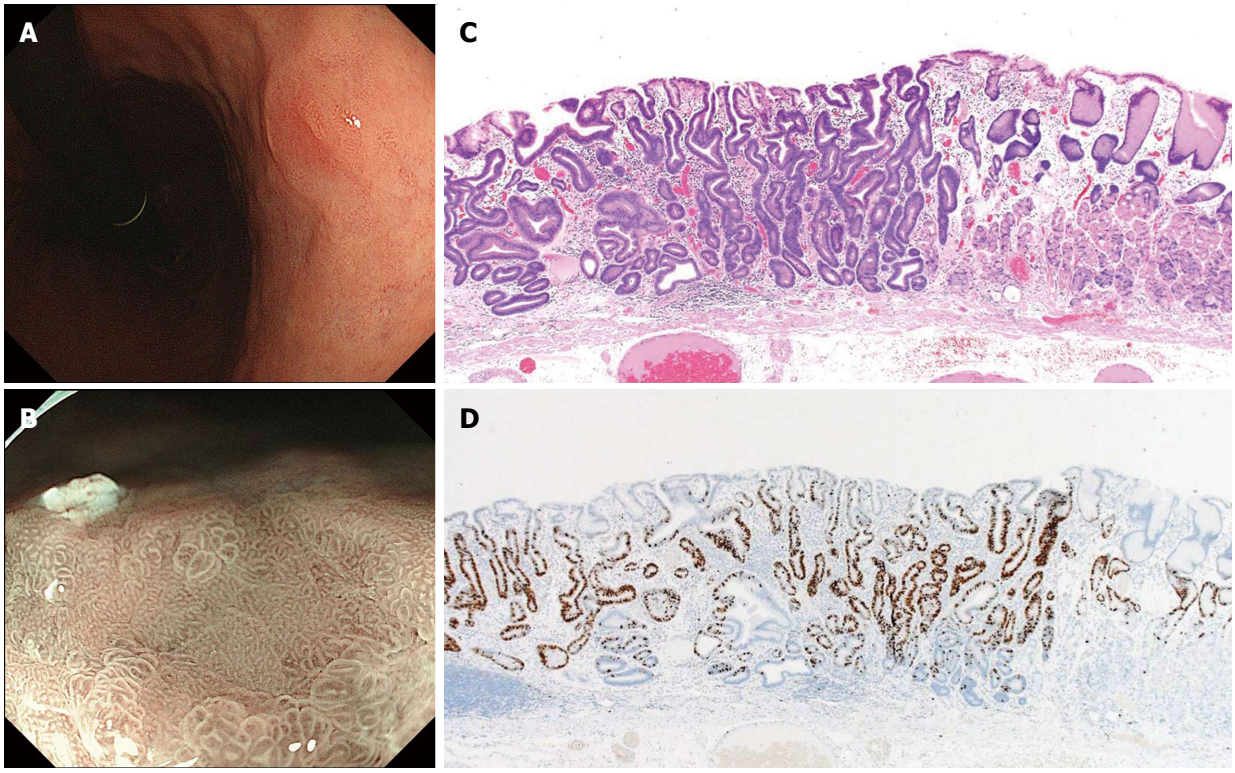

Figure 3 Differentiated-type early gastric cancer detected after successful *Helicobacter pylori* eradication. A: This endoscopic finding made qualitative cancer diagnosis difficult by conventional endoscopy; B: A "gastritis-like" appearance under narrow-band imaging with magnified endoscopy was demonstrated by a microsurface structure comprised of mixed pits and papillae, resembling the surrounding non-cancerous mucosa; C: Well-differentiated tubular adenocarcinoma with low-grade atypia (hematoxylin and eosin staining); D: Ki-67 positive cells localized in the middle-to-lower portion of the mucosa, indicating cytological maturation at the luminal surface layer of the cancer[47].

eradication[44]. Histological differentiation toward the surface layer of cancer tubules was characteristic when inflammatory activity was controlled by eradication, especially in differentiated-type adenocarcinomas with low-grade atypia. Because NBI-ME is a special modality for enhanced microvessel and microstructure visualization within the superficial layer of the gastric mucosa, these gastric cancers showed a "gastritis-like" appearance under NBI-ME[44]. The gastritis-like appearance revealed homogeneous and regular microstructure that was bordered by a clear white zone, resembling the adjacent non-cancerous mucosa. Recently, we further evaluated 100 early gastric cancers detected in 84 patients who received successful *H. pylori* eradication therapy[47]. The gastritis-like appearance in those cases was consistent with non-neoplastic superficial epithelium and histological surface differentiation. Surface differentiation led to difficulty in qualitative cancer diagnosis by NBI-ME (Figure 3)[47], and non-neoplastic superficial tubules on the cancer also caused unclear demarcation between the cancer and the surrounding gastric mucosa (Figure 4)[47]. Saka

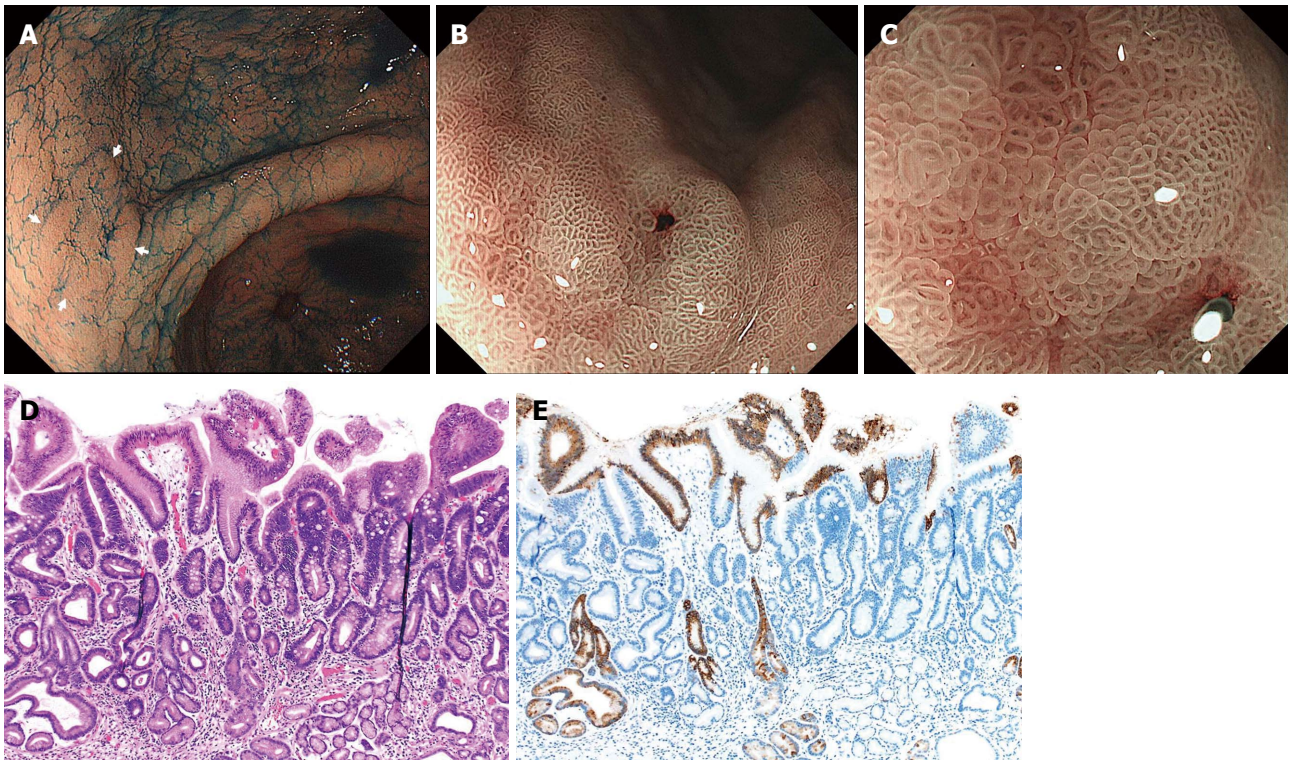

Figure 4 Differentiated-type early gastric cancer detected after successful *Helicobacter pylori* eradication. A: Chromoendoscopy revealed a depressed-type lesion in the anterior wall of the antrum; B, C: Narrow-band imaging with magnified endoscopy shows a "gastritis-like" appearance with a microsurface structure comprising of regular papillae resembling with unclear demarcation between the cancer and surrounding gastritis mucosa; D: Well-differentiated tubular adenocarcinoma with low-grade atypia (hematoxylin and eosin staining); E: MUC5AC immunohistochemical staining demonstrates that superficial non-neoplastic epithelium is interspersed among and above the cancer tubules[47].

et al[48] also reported that a gastritis-like appearance was apparent by conventional endoscopy and NBI-ME. In the endoscopic surveillance of early gastric cancer, NBI-ME diagnosis of a gastritis-like appearance should be considered as potentially cancerous among patients who have undergone successful eradication therapy. Identification of histological alteration in the surface layer of cancer tubules, which produce a gastritis-like appearance under NBI-ME, offers a promising approach for the accurate diagnosis of early gastric cancers after successful *H. pylori* eradication.

SURVEILLANCE FOR EARLY DETECTION OF GASTRIC CANCER AFTER *H. PYLORI* ERADICATION

Gastric cancer is often difficult to diagnose by endoscopy after successful *H. pylori* eradication therapy because of its indistinct border and lack of obvious cancerous features. Ito *et al*[49] have reported a significant difference in tumor stages between patients from Japan and other countries; however, even in Japan, some patients (5/81; 6.2%) were diagnosed at a more advanced stage during regular surveillance endoscopy after *H. pylori* eradication. We must therefore be vigilant for delayed diagnosis of early gastric cancer, caused by changes in the typical morphology. Although the growth rate of gastric cancer differs between tumors, most cancers are likely to have been present for several years before detection by endoscopic examination. We reported our experience of a patient with gastric cancer that progressed after eradication therapy (Figure 5)[26], ultimately requiring treatment by gastrectomy. After reviewing her previous endoscopic images, we noted that this lesion could have been discovered at an early stage up to three years before her diagnosis. In addition, because of the low-grade histological atypia, it was hard to diagnose accurately by biopsy taken before 1 year. Therefore, we recommend careful evaluation by endoscopists and pathologists alike when performing surveillance endoscopy and biopsies for patients after *H. pylori* eradication. The cytological differentiation in the surface layer of cancer tubules was a pathognomonic feature of the gastric mucin phenotype observed in differentiated adenocarcinomas with low-grade atypia. Although the ultimate goal of gastric cancer prevention is to decrease the associated mortality, surveillance endoscopy should be able to discover cancer at an early stage to facilitate treatment by ER rather than open surgery, which, in turn, should improve the quality of life for patients.

Previous studies reported the risk factors of primary or secondary cancer development after eradication to include old age[50-52], advanced atrophic change in

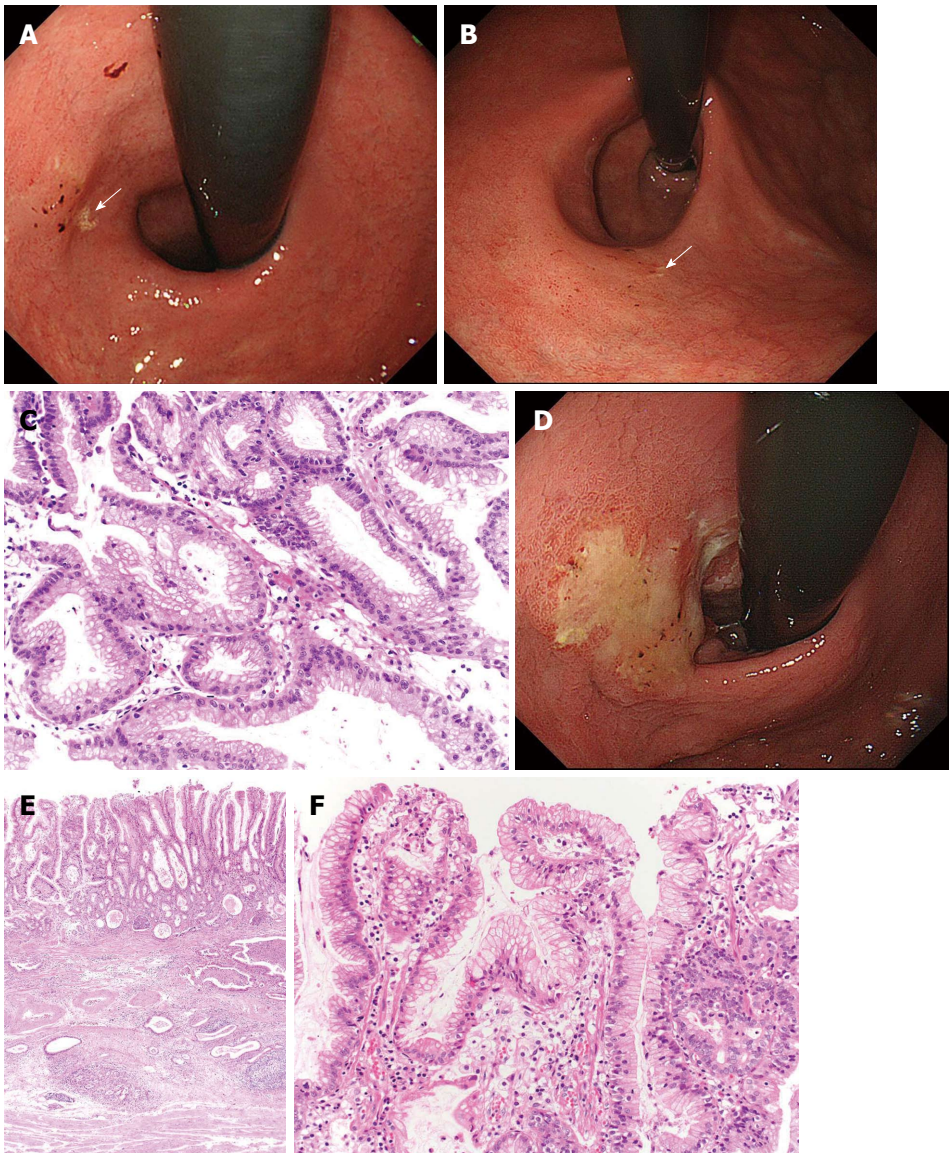

Figure 5 Gastric cancer progressed after eradication therapy. A: A review of the endoscopic pictures taken 3 years earlier revealed the presence of a discolored and flat elevated lesion adjacent to a xanthoma (arrow) in the cardia; B: This lesion was not clear yet, but the xanthoma had almost disappeared (arrow); C: The biopsy specimen taken from the lesion showed foveolar-type epithelium with mild structural atypia; D: After follow-up for 1 yr, the tumor had become evident and covered by mucus; E: The tumor had invaded into the deep submucosal layer, but the mucosal element was preserved; F: This cancer showed a gastric mucin phenotype with low-grade atypia[26].

the gastric corpus[17,40,53,54] and intestinal metaplasia distribution[55]. However, we showed that gastric cancer is often found by endoscopic examination in patients with synchronous gastric cancers, regardless of eradication therapy[26,33]. It remains uncertain whether *H. pylori* eradication can reverse atrophic gastritis and intestinal metaplasia, or whether it can prevent the progression to gastric cancer. Therefore, regular endoscopic surveillance should be beneficial in high-risk groups, provided it is performed at intervals of 3, 6, and 12 mo after initial ER, and every year thereafter for at least 10 years[26,33,56]. The next important clinical issue for the cancer survey program in East Asian countries might be to clarify the endoscopic appearance and biological behaviors of gastric cancers discovered after *H. pylori* eradication. To be able to diagnose these new gastric cancers effectively, we must establish more useful endoscopic examination methodologies.

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