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Review Article

Characteristics and Early Diagnosis of Gastric Cancer Discovered after *Helicobacter pylori* Eradication

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The prevalence of gastric cancer after eradication (GCAE) is increasing dramatically in Japan. GCAE has characteristic features, and we must understand these features in endoscopic examinations. Differentiated cancer types were frequently found after eradication and included characteristic endoscopic features such as reddish depression (RD). However, benign RD can be difficult to distinguish from gastric cancer because of histological alterations in the surface structures (nonneoplastic epithelium or epithelium with low-grade atypia [ELA]) as well as multiple appearances of RD. Recently, we clarified similar alterations in genetic mutations between ELA and gastric cancer, suggesting that ELA is derived from gastric cancer. Clinically, submucosal invasive cancer was frequently found in patients after eradication therapy even if they received annual endoscopic surveillance. We can improve the diagnostic ability using image-enhanced endoscopy with magnified observation. **(Gut Liver 2021;15:338-345)**

Key Words: Stomach neoplasms; Eradication therapy; *Helicobacter pylori*; Reddish depression; Epithelium with low-grade atypia

INTRODUCTION

Gastric cancer is the fifth most common cancer and the third leading cause of cancer death worldwide, accounting for nearly three-quarters a million deaths annually.[1] *Helicobacter pylori* infection plays an important role in gastric carcinogenesis. In 1994, the International Agency for Research on Cancer recognized that *H. pylori* is a definite carcinogen for gastric cancer development.[2] In Japan, Uemura *et al*.[3] demonstrated that gastric cancer developed only in patients with *H. pylori* infection using a prospective cohort study. We retrospectively reviewed our gastric cancer patients and demonstrated that the prevalence of *H. pylori*-negative gastric cancer was extremely rare (0.66%, 21/3,161).[4] In addition, Ono *et al*.[5] reported prevalence of *H. pylori*-negative gastric cancer was less than 1% in Japanese patients. These studies indicated that *H. pylori* infection is a crucial factor in gastric carcinogenesis in Japan.

In 2013, the Japanese government approved that national health insurance can cover *H. pylori* eradication therapy for patients with *H. pylori*-associated gastritis. For diagnosis of *H. pylori*-associated gastritis, endoscopic diagnosis of *H. pylori*-induced gastritis is essential prior to eradication therapy. At present, 1.5 million courses of eradication therapy have been carried out in Japan.[6] This indicates that primary prevention of gastric cancer has started in Japan.

Along with the increase in eradication therapy, mortality from gastric cancer is now decreasing gradually. However, eradication therapy has caused another crucial problem, namely the problem of gastric cancer after eradication therapy (GCAE). Gastric cancer develops in some patients even after successful eradication therapy, and recent studies have been clarifying its characteristic features. In the present review, we examine some problems around GCAE and propose effective clinical practices for the diagnosis and treatment for GCAE.

PREVALENCE OF GASTRIC CANCER DISCOVERED AFTER ERADICATION THERAPY

Many studies have indicated that eradication therapy for *H. pylori* diminishes the prevalence of gastric cancer development.[7] In 1997, Uemura *et al*.[8] demonstrated that the prevalence of gastric cancer decreased in patients with successful eradication therapy in a non-randomized prospective study. In 2008, the results of a Japanese multicenter study were published and demonstrated the prevalence of secondary gastric cancer diminished by one-third using successful eradication therapy.[9] Recently, the effect of eradication therapy has been shown in some systematic reviews from Western countries as well as from East Asia including Japan.[10-14] Lee *et al*.[10] demonstrated that eradication provided significant benefit for asymptomatic infected individuals (pooled incidence rate ratio, 0.62; 95% confidence interval [CI], 0.49 to 0.79) and individuals after endoscopic resection of gastric cancers (pooled incidence rate ratio, 0.46; 95% CI, 0.35 to 0.60). Likewise, Doorakkers *et al*.[11] showed the pooled relative risk of gastric cancer was 0.46 (95% CI, 0.32 to 0.66) favoring eradication therapy. Sugano[14] also demonstrated that a *H. pylori* eradication group showed a significantly lower risk of gastric cancer development (odds ratio [OR], 0.46; 95% CI, 0.39 to 0.55), and especially emphasized that the beneficial effect of eradication was greater in Japan (OR, 0.39; 95% CI, 0.31 to 0.49). Most recently, a Korean prospective, double-blind, placebo-controlled, randomized trial clearly showed that patients with early gastric cancer who received *H. pylori* treatment had lower rates of metachronous gastric cancer (hazard ratio in the treatment group, 0.50; 95% CI, 0.26 to 0.94; p=0.03).[15]

WHEN DID GASTRIC CANCER DEVELOP IN PATIENTS AFTER SUCCESSFUL ERADICATION?

First of all, we have to understand the pathogenesis of GCAE. Did GCAE newly develop after eradication therapy or was it already existing before eradication therapy? Clinical features in cases with GCAE, especially the gender of patients and tumor location in the stomach, were reported to be similar to those with conventional gastric cancer (with *H. pylori* infection)[16] but different from those without *H. pylori* infection.[17] In addition, the natural history of mucosal gastric cancer with differentiated histology was reported as slow-growing as expected, for example, doubling time was reported as 16.6 months by radiological evaluation.[18,19] These findings strongly suggested that the majority of GCAE, detected in the present real-world study, had already developed before eradication therapy.[20]

ENDOSCOPIC FEATURES OF GASTRIC CANCER DISCOVERED AFTER ERADICATION THERAPY

We have to recognize that GCAE revealed representative endoscopic feature, namely a superficial depressed feature.[16,21-23] In 2005, we reported the morphological alterations of gastric tumors after eradication therapy of *H. pylori* in a prospective intervention study.[24] Patients with a gastric tumor received eradication therapy and the features of the gastric tumors were re-examined. Surprisingly, after successful eradication, 50% adenomas and 24% adenocarcinoma became flat and indistinct.[24] This phenomenon seemed to be compatible with the endoscopic features of GCAE.

The true pathogenesis of tumor flattering is still unknown. We speculated that a decreased level of serum gastrin may be a reason for this phenomenon. Gastrin is a growth factor for epithelial cells,[25,26] and we previously detected the gastric receptor in gastric epithelial cells and gastric cancer cells.[27,28] Serum gastrin levels were decreased by eradication therapy in patients with atrophic gastritis;[29] therefore, proliferating signals through the gastrin receptor may decline in response to the eradication system followed by flattering the tumor tissue.[30] Decreases in cytokine levels in response to eradication therapy may be another reason for the inhibition of tumor growth and flattering of the tumor tissue.[31,32]

HISTOLOGIC FEATURES OF GASTRIC CANCER DISCOVERED AFTER ERADICATION THERAPY

We further found that endoscopic alteration was closely linked to histological features. After eradication, a normal or mild-atypical epithelium appeared on the surface of gastric tumor tissues just covering the tumor tissue.[30] After eradication, we found almost normal epithelium on the surface of adenoma tissue and slightly atypical epithelium on the surface of gastric cancer tissue.[30] This may be a reason why gastric tumors become indistinct after eradication therapy.

In cases with gastric adenoma, Gotoda *et al*.[33] first reported indistinct features after eradication therapy. In our previous study, 50% of gastric adenomas became indistinct and normal epithelium appeared in 75% of all adenomas.[34] Recently, Suzuki *et al*.[35] reported that 26% of adenomas revealed histological complete regression after eradication therapy.

On the other hand, we could find slightly atypical (not completely normal) epithelium covering gastric cancer

tissue (Fig. 1). We named this feature as epithelium with low-grade atypia (ELA) and defined it according to the following criteria: (1) ELA must lie on the surface of gastric cancer tissue; (2) ELA must be columnar epithelium with spindle or oval nuclei; (3) nuclear polarity must be present in the ELA; and (4) the ELA must be separated and distinguished from the surrounding nonneoplastic mucosa.[36] Previously, we have presented that ELA appeared not only on gastric cancer after *H. pylori*-eradication but on that with *H. pylori* infection. However, the degree of ELA was statistically higher on *H. pylori*-eradicated cancer than on *H. pylori*-infected cancer.[36] These histological features were confirmed in several studies mainly from Japan, and this histology was also called "nonneoplastic epithelium."[37-39]

Furthermore, we examined the pathogenesis of this epithelium. Small numbers of nonneoplastic glands were detected within the gastric cancer tissue, and these glands were recognized as nonneoplastic without difficulty. However, we also detected another type of epithelium termed ELA, which was different from both nonneoplastic epithelium and tumor tissue, on the tumor surface. It should be clarified whether ELA comes from normal tissue (indicating that ELA is from regenerative changes from nonneoplastic epithelium) or tumor tissue (where ELA comes from the re-differentiation of gastric cancer by eradication). We extracted DNA from gastric cancer tissue, normal gastric mucosa, and ELA by laser-microdissection.[40] We used the NCC Oncopanel (National Cancer Center and Sysmex Cancer Innovation Laboratory, Tokyo, Japan) and examined gene alterations for 125 genes using deep-sequencing.[41] The mutation profile of ELA was quite similar to that in gastric cancer tissue, suggesting that ELA was derived from gastric cancer tissue, and gastric cancer tissue can be histologically restored by eradication therapy. ELA was not from normal epithelium contaminating the tumor tissue but from gastric cancer tissue. In animal model, adenocarcinoma tissue can be restored by genetic manipulation.[42] This may be a first report describing that human gastric cancer tissue can be histologically restored by eradication therapy.

CLINICAL IMPACT OF HISTOLOGICAL CHARACTERISTICS IN THE DIAGNOSIS GASTRIC CANCER DISCOVERED AFTER ERADICATION THERAPY

Clinically, this phenomenon is supposed to evoke the difficulty in endoscopic diagnosis of GCAE as well as the gastric adenomas described above. Previously, we reported that submucosal invasive GCAE showed extensive ELA on the surface of gastric cancer tissue in patients receiving annual endoscopic examination after eradication.[36] The appearance of ELA may interrupt the detection of GCAE in earlier stages, as a result these tumors are likely to be detected at more advanced stages. Moreover, it has been reported that there is a noticeably increased prevalence of GCAE showing submucosal invasion compared with that for *H. pylori*-positive cancers.[43-45]

Thereafter, we retrospectively analyzed the clinicopathological characteristics of GCAE patients who received annual endoscopic examinations after eradication, and compared incident of gastric cancer with submucosal invasion between GCAE and controls. The prevalence of early gastric cancer with submucosal invasion was significantly higher in the eradicated group than in the control group after propensity score matching (16.0% vs 4.9%, respectively; p=0.021) (Table 1).[45,46] We could not detect a statistically significant difference in any features, including sex, age, previous cancer history, location, macroscopic type, and tumor size between two groups.[46] *H. pylori* eradication therapy increased the prevalence of differentiated-type

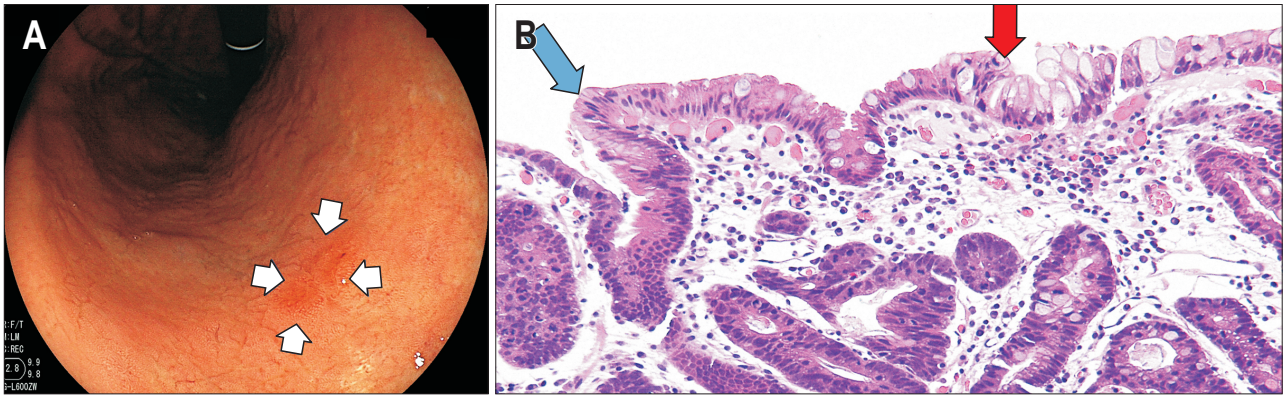

Fig. 1. The patient was a woman in her 60s. (A) A reddish depressed lesion (arrows) was observed on the lesser curvature of the gastric corpus. (B) Histologically, low-grade atypia (between the blue and red arrows) covered the surface of the tumor tissue. Tumor tissue and normal epithelium were noted on the left side of the blue arrow and on the right side of the red arrow, respectively.

gastric cancer with submucosal invasion despite patients' completion of annual endoscopic screening after eradication.

IMPORTANCE OF EARLY DETECTION OF GASTRIC CANCER DISCOVERED AFTER ERADICATION BY ENDOSCOPIC SURVEILLANCE

For accurate endoscopic examination in patients with successful eradication, we have to understand that the typical endoscopic features of GCAE were reddish depression (RD). Diffuse redness, which is a typical feature of *H. pylori*-associated gastritis,[47] disappears after successful eradication, and cancer lesions become relatively reddish. However, these RDs can also be found in non-cancer stomachs and are termed mottled patchy redness[48] or map-like redness.[49] Although these lesions were reported to be frequently found in patients with gastric cancer,[50] it should be mentioned these were not direct findings of gastric cancer itself.

First, we tried to diagnose malignant RD lesions (RDLs) with white-light imaging (WLI) based on reports described by Yao *et al*.[51] Gastric biopsy was performed in patients in whom we identified an irregularity (heterogeneous color, irregular demarcation or spiny depressed lesion) in RDLs; however, positive predictive value of a gastric biopsy was only 1.7%.[52] Next, we used magnifying narrow-band imaging (M-NBI) to diagnose RDL. Based on the vessel plus surface classification system,[53] we evaluated microsurface pattern (MSP; regular or irregular) and microvascular pattern (MVP; regular, irregular or absent) as we reported previously.[54] We performed gastric biopsy when the RDLs

Table 1. Prevalence of SM Invasive Cancer Discovered after Eradication Therapy

Depth (SM invasion)	Eradicated	Control	p-value
Maehata *et al.*[45]	17/96 (18)	8/96 (8)	0.051
Hata *et al.*[46]	13/81 (16)	4/81 (5)	0.021

Data are presented as number/number (%).
SM, submucosal.

Table 2. Comparison of the Diagnostic Efficacy of White Light Imaging and Magnifying NBI for GCAE

	Using white light imaging (n=117)	Using magnifying NBI (n=104)
Lesions needed biopsy	83/117 (71)*	21/104 (20)*
Positive predictive value of biopsy	2/83 (2)*	9/21 (43)*

Data are presented as number/number (%).
NBI, narrow-band imaging; GCAE, gastric cancer after eradication.
*p<0.01 (between two groups).

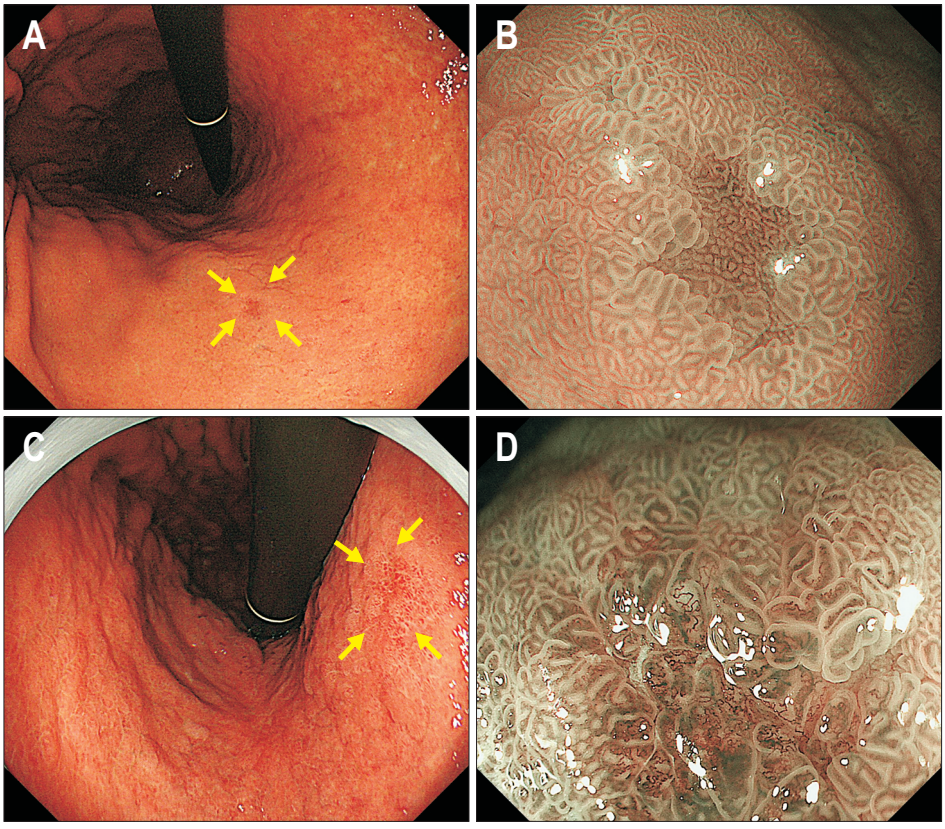

Fig. 2. The patients were a woman in her 60s without gastric cancer (A, B) and a man in his 60s with gastric cancer (well-differentiated tubular adenocarcinoma; C, D). Endoscopic image of a reddish depressed lesion acquired by white light endoscopy (A, C; indicated by the yellow arrows). By using magnifying narrow-band imaging, regular (B) or irregular (D) microsurface pattern and microvascular pattern were observed in each lesion.

revealed an irregular MSP and/or irregular MVP within the demarcation line (Fig. 2).

In the M-NBI group, biopsy was performed in 21 patients (20%), and nine were diagnosed as adenocarcinoma. Biopsy was required in fewer patients, and the positive predictive value of biopsy was statistically higher in the M-NBI group than in the WLI group (Table 2).[52] These findings suggested that M-NBI demonstrated significantly superior diagnostic efficacy with respect to RDL to select malignant RD endoscopically. However, it may be difficult to diagnose these lesions only by WLI at present. For accurate diagnosis, we reported the usefulness of magnifying NBI methods. Recently, several reports from Japan described the usefulness of image-enhanced endoscopy in the diagnosis of GCAE.[55-57]

POSSIBLE RISK STRATIFICATION FOR DEVELOPMENT OF GASTRIC CANCER DISCOVERED AFTER ERADICATION THERAPY AND EFFECTIVE SURVEILLANCE

The final goal of our strategy was to diminish mortality from gastric cancer. Primary prevention by eradication therapy may be the best way to achieve our goal. The Japanese Society of Helicobacter Research demonstrated a total care program against *H. pylori* infection and gastric cancer screening.[58] Careful follow-up will be necessary even after eradication therapy.

Risk stratification should be helpful for supplying effective surveillance of patients after eradication. Atrophic gastritis in the corpus or intestinal metaplasia is considered to be a risk factor for the development of GCAE.[59-64] In 2015, the Kyoto Global Consensus Conference on *H. pylori* gastritis was held and the following statement was accepted: patients who remain at risk, as defined by the extent and severity of atrophy, should be offered endoscopic and histological surveillance (grade of recommendation: strong, evidence level: high, consensus level: 97.3%).[65] In these cases, annual endoscopic surveillance may be necessary for early detection of gastric cancer.

In Japan, test-and-treat for *H. pylori* infection has spread in younger generations. This may be the best way to diminish gastric cancer death, however, the proper surveillance is not established for these subjects. Since these have little risk for gastric cancer development, annual endoscopic examination may be inappropriate. Recently, a molecular marker associated with DNA methylation has been investigated, and we hope a possible marker for the risk stratification and may be applied for these subjects in the near future.[66-69]

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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