Digestion

Review

Digestion 2022;103:54–61
DOI: 10.1159/000519838

Received: July 30, 2021
Accepted: September 22, 2021
Published online: November 2, 2021

Detection of Early Gastric Cancer after *Helicobacter pylori* Eradication

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Keywords
Gastric cancer · *Helicobacter pylori* · Eradication · Characteristics · Predictor

Abstract
Background: Based on evidence that *Helicobacter pylori* eradication reduces the development of gastric cancer and other diseases such as peptic ulcer, eradication therapy has prevailed. However, gastric cancer can develop even after successful eradication. ***Summary:*** In this review article, we searched for studies that identified the characteristics of primary and metachronous gastric cancers after *H. pylori* eradication, the risk factors for the development of these cancers after successful *H. pylori* eradication, and whether image-enhanced endoscopy is useful for diagnosing gastric cancer after eradication. A gastritis-like appearance is seen as a characteristic endoscopic finding, which corresponds to an epithelium with low-grade atypia – also known as nonneoplastic epithelium – covering the surface of the cancerous glands. This finding may make endoscopic detection of early gastric cancer difficult after *H. pylori* eradication. Similar risk factors, such as the male sex, endoscopic atrophy, histologic intestinal metaplasia, and late eradication, have been reported as predictors for the development of both primary and metachronous gastric cancers. Image-enhanced endoscopy, such as linked color imaging, may be useful for the detection and risk stratification of gastric cancer after eradication. ***Key Messages:*** Based on these findings, we believe that effective surveillance of high-risk patients leads to early detection of gastric cancer in the era of *H. pylori* eradication.

Introduction

Gastric cancer is one of the deadliest malignancies worldwide, with 1 million new cases reported annually, as mentioned in Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) 2020. *Helicobacter pylori* was first isolated by Warren and Marshall [1], and because of its close association with the development of gastric cancer [2], it was later recognized as a definite carcinogen [3]. Even before the discovery of *H. pylori*, Correa et al. [4] proposed a cascade for gastric cancer development where gastritis leads to atrophic gastritis, intestinal metaplasia, and finally gastric cancer. *H. pylori* was recognized as a causative agent for Correa's cascade [5].

H. pylori eradication therapy was first identified as an effective treatment for peptic ulcers, after which several studies evaluated its relationship with the development of

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gastric cancer. Through a randomized controlled trial in 2008, Fukase et al. [6] showed that *H. pylori* eradication therapy reduced metachronous gastric cancer development after endoscopic resection for gastric cancer. A similar study from Korea in 2018 showed that eradication therapy had a positive effect on reducing metachronous gastric cancer [7]. Other systematic reviews and meta-analyses showed that *H. pylori* eradication reduced not only metachronous but also primary, gastric cancer [8–10]. Based on these findings, eradication therapy has drastically prevailed. In 2013, Japan became the first nation in the world to provide national health insurance coverage for *H. pylori* gastritis eradication therapy. However, gastric cancer still develops, even after *H. pylori* eradication therapy, thus becoming a major issue. Early detection is crucial for good prognosis of gastric cancer. Thus, risk stratification of gastric cancer after eradication is an important clinical issue for the effective surveillance of high-risk populations. Furthermore, to effectively detect gastric cancer after eradication therapy, knowledge of the features of gastric cancer and effective methodology is essential.

In 2018, we extensively reviewed articles about (1) the characteristics of gastric cancer that developed after *H. pylori* eradication therapy and (2) the predictors of primary gastric cancer after eradication therapy [11]. Here, we briefly summarize and update these points. Furthermore, we review articles about metachronous gastric cancer and the usefulness of image-enhanced endoscopy for diagnosing gastric cancer after *H. pylori* eradication.

Characteristics of Gastric Cancer after *H. pylori* Eradication

Kitamura et al. [12] described an epithelium with low-grade atypia (ELA) covering gastric cancer tissue after *H. pylori* eradication. According to these authors, for ELA to be considered present, (1) the ELA must lie on the surface of gastric cancer tissue, (2) the 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 non-neoplastic mucosa. They reported that ELA that was continuous with the gastric tumor was detected in 22 of 27 cases (81%) of patients who had successfully undergone *H. pylori* eradication therapy – a significantly greater percentage than that observed in controls (10 of 27) ($p < 0.01$).

Saka et al. [13] described a nonneoplastic epithelium covering cancerous areas in gastric cancer after eradication. The nonneoplastic epithelium covered >10% of the cancerous area more frequently in the eradication group (15/24 vs. 3/47). Furthermore, in the eradication group, >90% of cancers showing a gastritis-like appearance had a nonneoplastic epithelium extending over 10% of the cancerous area. "Gastritis-like appearance" was initially reported by Kobayashi et al. [14]. They defined "gastritis-like appearance" under magnified narrow-band imaging endoscopy after eradication as an orderly microsurface structure and/or loss of clear demarcation with resemblance to the adjacent, noncancerous mucosa. The frequency of a gastritis-like appearance was 44% (22/50) in the eradication group, which was significantly higher than that in the control group (4% [2/50], $p < 0.001$). In the eradication group, the gastritis-like appearance was significantly correlated with histological surface differentiation ($p < 0.001$).

Not only a gastritis-like appearance but also a depressed appearance is well known as an endoscopic feature of gastric cancer after eradication. Kamada et al. [15] reported that among 20 gastric cancer cases discovered in eradicated patients, 18 (90%) were ulcer type. Another report on endoscopic submucosal dissection cases showed that 81% (78 of 96) of early gastric cancer from eradicated patients were depressed type – a significantly higher proportion than the 53% (51 out of 96) in *H. pylori* (noneradicated)-infected patients [16].

Risk Factors for Primary Gastric Cancer after *H. pylori* Eradication

Endoscopic Atrophy

There are many reports on the association between endoscopic atrophy and gastric cancer, especially in Japan. Kimura and Takemoto [17] first described the classification of endoscopic atrophy – that is, severity of atrophy – in 1969, and their classification is still widely used. Atrophic gastritis was graded as C1, C2, C3, O1, O2, and O3 according to the extent of atrophy. C1, C2, and C3 were classified as closed type, while O1, O2, and O3 were classified as open type. Later, C0 was added as a classification for those without atrophic gastritis. In 2001, Uemura et al. [2] reported that severe endoscopic atrophy was a predictor for primary gastric cancer in patients with *H. pylori* infection. To date, several cohort studies have shown an association between endoscopic atrophy and gastric cancer after *H. pylori* eradication.

In 2016, we reported a cohort study of 573 *H. pylori*-eradicated cases, of which 288 (50%) were eradicated for

gastritis [18]. During the follow-up period of 6.2 ± 4.8 years, 21 primary gastric cancers developed. The cumulative incidences of gastric cancer in the none/mild (C0–C2), moderate (C3 and O1), and severe (O2 and O3) atrophy groups were 0.7%, 0%, and 2% at 1 year; 0.7%, 1.9%, and 10% at 5 years; and 0.7%, 3.4%, and 16% at 10 years, respectively.

Take et al. [19] reported a cohort study (with a mean follow-up of 9.9 years after successful eradication) of 1,222 consecutive patients with peptic ulcer diseases in 2015. Gastric cancer developed in 21 of the 1,030 patients, and endoscopic atrophy and age were significantly associated with the development of gastric cancer after *H. pylori* was eradicated.

A 2020 retrospective cohort study of 2,737 patients (of which 2,193 were males and 2199 were eradicated for peptic ulcer) compared the gastric cancer risk in the second decade of follow-up with that in the first decade [20]. During the follow-up period (a maximum of 21.4 years and a mean of 7.1 years), gastric cancer developed in 9 of the 801 patients with mild atrophy (0.15% per year), 23 of the 1,090 with moderate atrophy (0.29% per year), and 36 of the 846 with severe atrophy (0.67% per year) ($p \leq 0.001$, log-rank test). In fact, it was shown that gastric cancer can develop even 18.3 years after successful eradication therapy. Furthermore, risk of gastric cancer incidence in the second decade compared with that of the first decade was high for diffuse-type gastric cancer with mild or moderate gastric atrophy, while the incidence risk for intestinal- or diffuse-type cancers in patients with severe atrophy did not change significantly, even though they were at the highest risk. The study concluded that endoscopic surveillance should be performed beyond 10 years after a patient had been cured of *H. pylori*, irrespective of the severity of gastric atrophy.

Toyoshima et al. [21] also reported a cohort study with a mean follow-up of 2.46 years: 15 gastric cancers developed in 1,232 patients after *H. pylori* infection had been eradicated. Patient age and grade of endoscopic atrophy were associated with gastric cancer development.

Histologic Intestinal Metaplasia

In the abovementioned 2016 cohort study [18], in which 21 gastric cancers developed in 573 successful eradication therapy cases, we were the first to show an association between histologic intestinal metaplasia and future gastric cancer development after *H. pylori* eradication. Participants were evaluated for the presence of histologic intestinal metaplasia through biopsies of both the antrum and corpus. Compared to the group with no intestinal metaplasia, patients with metaplasia limited to the antrum had a 4.5-fold increased risk and those with metaplasia in the corpus had a 7.6-fold increased risk of developing gastric cancer.

Kodama et al. [22] reported a case-control study of an *H. pylori*-eradicated cohort. During the mean follow-up period of 2.4 years, 33 gastric cancers developed in 2,355 patients who underwent endoscopy after successful eradication. Among them, 21 patients with gastric cancer and 66 without cancer were analyzed. The patients were matched with respect to age and sex, and intestinal metaplasia scores – evaluated using the Updated Sydney System [23] – were significantly higher in the gastric cancer group.

Long-Term Use of Proton Pump Inhibitors

In 2018, Cheung et al. [24] reported an association between the long-term use of proton pump inhibitors (PPIs) and gastric cancer after *H. pylori* eradication. Clarithromycin-based triple therapy was administered to 63,397 patients until 2012; 153 gastric cancers developed by 2015, and the risk increased the longer the PPI was administered. The hazard ratios were 5.0, 6.7, and 8.3 for treatment durations of ≥1, 2, and 3 years, respectively. This is likely related to the profound acid suppression of PPIs that worsens atrophic gastritis, particularly in patients with established gastric atrophy due to chronic *H. pylori*-induced inflammation.

Recently, Seo et al. [25] investigated the association between PPIs and gastric cancer in Korea. In *H. pylori*-eradicated patients, the incidence of gastric cancer was significantly associated with PPI use of >180 days compared with no use of PPIs (PPI ≥180 days vs. non-PPI: 30/12,470 person-years vs. 9/7,814 person-years; hazard ratio, 2.22; 95% confidence interval, 1.05–4.67; $p = 0.036$). The authors concluded that long-term PPI treatment should be administered with caution in regions where the risk of gastric cancer was high. Of course, these studies were observational in nature, and interpretation of results warrants further investigation.

Risk Factors for Metachronous Gastric Cancer after *H. pylori* Eradication

With the widespread use of endoscopic resection to treat gastric cancer [26], the issue of metachronous gastric cancer has become significant because the entire (high-risk) stomach remains after endoscopic resection. Table 1 summarizes the following studies that examined

Table 1. Risk factors for metachronous gastric cancer development after *H. pylori* eradication

Reference	Patients, *n*	Age	Follow-up period, years	Cancers, *n* (%)	Risk factor
Kim et al. [27]	7,452 ER	60	3.9	252 (3.4)	Late eradication (>1 year after resection), male, BMI, smoking
	12,315 surgeries		5.0	114 (0.9)	Late eradication (>1 year after resection), male, BMI, smoking
Yang et al. [29]	1,115 ER	64	4.2	82 (7.4) in 72 patients	Male, histologic IM in the corpus, synchronous neoplasm
Mori et al. [43]	594 ER	66	4.5	79 (13)	Male, severe endoscopic atrophy, location of initial GC (U), synchronous GC, smoking
Moribata et al. [32]	122 ER	69	3.9	22 (18)	Endoscopic IM, map-like redness
Bae et al. [31]	485 ER	62	5	34 (7)	Male
Kwon et al. [44]	214 ER	61	3.3	10 (4.7)	Age (≥60)
Maehata et al. [33]	177 ER	68	3	15 (8.5)	Severe endoscopic atrophy
Hanaoka et al. [34]	82 ER	65	4.6	12 (14.6)	Severe endoscopic atrophy
Shiotani et al. [45]	80 ER	66	2.8	9 (11.3)	Severe histologic atrophy at the corpus

H. pylori, Helicobacter pylori; ER, endoscopic resection; BMI, body mass index; IM, intestinal metaplasia; GC, gastric cancer.

Table 2. Usefulness of image-enhanced endoscopy for visualizing gastric cancer after *H. pylori* eradication

Reference	Study design	Findings
Diagnosis of gastric cancer after eradication		
Dohi et al. [39]	RCT	14 out of 14 gastric cancers were diagnosed by BLI-bright, while 2 out of 11 were diagnosed by WLI; subgroup analysis
Kitagawa et al. [40]	Randomly reviewed recorded videos	Miss rates were significantly lower with LCI than with WLI (30.7% vs. 64.9%, $p < 0.001$)
Risk factors of gastric cancer after eradication		
Majima et al. [41]	Cross-sectional study	Map-like redness was significantly more frequent in the cancer group than in the noncancer group and identified more frequently using LCI than WLI
Tahara et al. [42]	Cross-sectional study	Correlation between magnified NBI patterns and histologic intestinal metaplasia

H. pylori, Helicobacter pylori; RCT, randomized controlled trial; BLI-bright, blue laser image-bright; LCI, linked color imaging; WLI, white light imaging; NBI, narrow-band imaging.

the risk factors for metachronous gastric cancer after eradication therapy.

Kim et al. [27] conducted a cohort study using the Korean National Health Insurance Service database. They analyzed the data of patients who underwent endoscopic resection or partial gastrectomy for early gastric cancer and received *H. pylori* eradication therapy. The 5-year cumulative incidence of metachronous lesions after endoscopic resection was 14.0% in the pre-resection group, 12.3% in the within-1-year postresection group, and 16.9% in the >1-year postresection group. This positive effect of early eradication was similarly reported in a Taiwanese study wherein early eradication after peptic ulcer led to a decreased incidence of gastric cancer [28]. Other studies reported risk factors for metachronous gastric cancer to be the male sex [29–31], histologic [29] and endoscopic intestinal metaplasia [32], severe endoscopic atrophy [30, 33, 34], and smoking [30]. Most of these risk factors are also risk factors for primary gastric cancer after eradication or gastric cancer with current *H. pylori* infection.

All studies summarized in Table 1 are cohort studies with a follow-up period of 2.8–5.0 years. During this limited follow-up period, a high incidence of metachronous gastric cancer (3.4%–14.6%) after endoscopic resection was reported. Thus, even patients without risk factors should receive intensive surveillance.

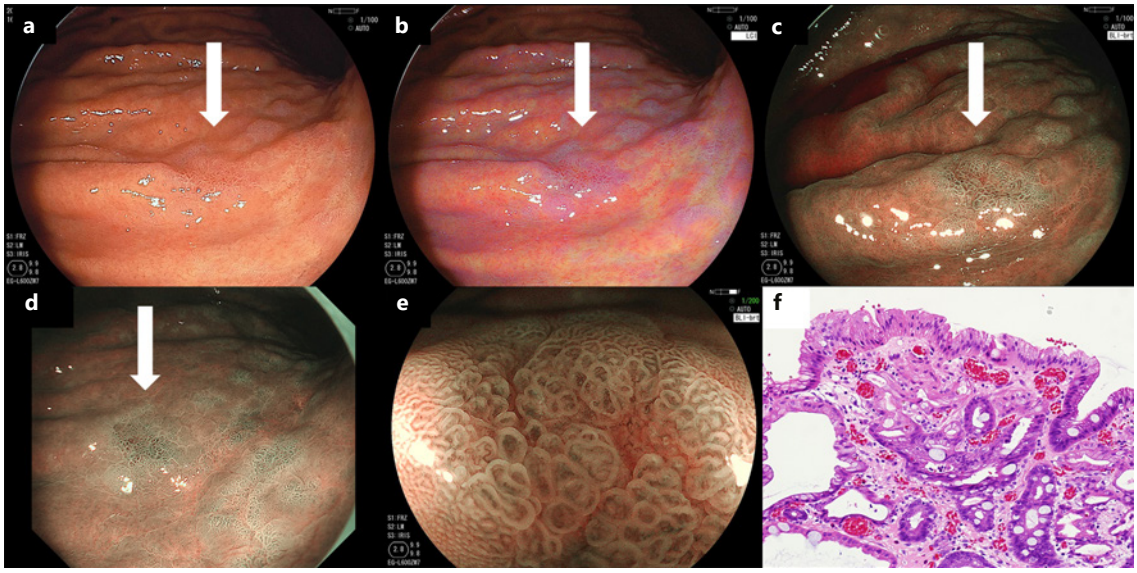

Fig. 1. Images of gastric cancer detected 20 years after successful *H. pylori* eradication, captured using different imaging techniques: white light imaging (**a**), linked color imaging (**b**), blue laser imaging-bright (**c**), narrow-band imaging (**d**), and magnifying blue laser imaging-bright (**e**). **f** Moderately differentiated tubular adenocarcinoma with low-grade atypia on the surface (HE; original magnification, ×200). *H. pylori, Helicobacter pylori.*

Comparison of Risk Factors for Primary and Metachronous Gastric Cancer after *H. pylori* Eradication

Endoscopic and histologic atrophy, histologic intestinal metaplasia, male sex, age, and late eradication have been reported to be risk factors for both primary and metachronous gastric cancer. To date, BMI, smoking, endoscopic intestinal metaplasia, and map-like redness have been reported as risk factors only for metachronous gastric cancer. However, reports regarding the risk factors of primary gastric cancer are limited, and further studies are warranted.

Usefulness of Image-Enhanced Endoscopy for Diagnosing Gastric Cancer after H. pylori Eradication

Several reports, as summarized in Table 2, have described the usefulness of image-enhanced endoscopy for diagnosing gastric cancer after *H. pylori* eradication.

Diagnosis of Gastric Cancer after Eradication

There are several reports on the usefulness of image-enhanced endoscopy (i.e., linked color imaging, narrow-band imaging, and i-scan optical enhancement) for gastric cancer detection before eradication [35–38]. However, there are limited reports regarding detection of gastric cancer after eradication by image-enhanced endoscopy.

Dohi et al. [39] conducted a randomized, controlled study in 2 Japanese academic centers. Patients at high risk for gastric cancer (follow-up endoscopy for atrophic gastritis with intestinal metaplasia or surveillance after endoscopic resection of early gastric cancer) were randomly assigned to receive primary white light imaging (WLI), followed by blue laser imaging-bright (BLI-bright) or primary BLI-bright followed by WLI (shown in Fig. 1). The real-time diagnostic rate of early gastric cancer with primary BLI-bright was significantly higher than that with primary WLI (93.1% vs. 50.0%). In subgroup analysis, gastric cancer after eradication was more effectively diagnosed using primary BLI-bright (14 out of 14) compared to primary WLI (2 out of 11) ($p < 0.001$). Thus, the effective diagnostic performance implies that BLI-bright may also be promising for gastric cancer detection after eradication.

Kitagawa et al. [40] compared the usefulness of linked color imaging (LCI) with WLI to detect gastric cancer after eradication. Six endoscopists reviewed recorded videos using both WLI and LCI for 70 consecutive patients after *H. pylori* eradication, among whom 19 had early gastric cancer in a randomized order. Miss rates were significantly lower with LCI than with WLI (30.7% vs. 64.9%, $p < 0.001$).

Risk Stratification of Gastric Cancer after Eradication

Majima et al. [41] conducted a cross-sectional study to evaluate background mucosa-associated endoscopic

Table 3. Comparison of general gastric cancer risk factors and characteristic endoscopic findings with those specific to *H. pylori*-eradicated patients

Overall		After eradication
Risk factors for gastric cancer		
Primary gastric cancer	*H. pylori* infection Age Male Smoking Histologic atrophic gastritis Histologic intestinal metaplasia OLGA staging OLGIM staging Severe endoscopic atrophy Endoscopic intestinal metaplasia Enlarged fold Nodularity Pepsinogen I ≤70.0 and pepsinogen I/II ratio ≤3.0 Proton pump inhibitor	Age Male OLGA staging Severe endoscopic atrophy Pepsinogen I/II ratio ≤4.5 Proton pump inhibitor
Metachronous gastric cancer	*H. pylori* infection Male Smoking Histologic intestinal metaplasia Histologic neutrophil infiltration Severe endoscopic atrophy Synchronous neoplasia Pepsinogen I/II ratio ≤3.0	Late eradication Age Male Body mass index Smoking Histologic intestinal metaplasia Severe histologic atrophy at the corpus Severe endoscopic atrophy Synchronous neoplasm Location of initial gastric cancer Map-like redness
Characteristic endoscopic findings	Mucosal discoloration (erythema or pallor) Morphological changes of the mucosal surface (protruding, elevated, or depressed) Tapered or interrupted mucosal folds Spontaneous bleeding	Depressed Relatively small Gastritis-like appearance

findings described in the Kyoto classification of gastritis. They evaluated the background mucosa of patients after successful eradication with and without gastric cancer. Map-like redness was observed significantly more frequently in the cancer group than in the non-cancer group using WLI (61.5% vs. 37.7%, $p = 0.001$) and LCI (78.0% vs. 45.9%, $p < 0.001$), and identified more frequently using LCI than WLI.

Tahara et al. [42] divided magnifying narrow-band imaging patterns in the gastric body into 2 types: restored-small, round pits, accompanied with honeycomb-like subepithelial capillary networks (restored type) and atrophic-well demarcated oval or tubulovillous pits with clearly visible or wavy vessels (atrophic type). Among the 125 patients assessed after eradication, sensitivity and specificity for the atrophic type for detection of histological intestinal metaplasia – which is a well-established risk factor for gastric cancer – were as high as 95.9% and 98.3%, respectively.

Comparison of General Gastric Cancer Risk Factors and Characteristic Endoscopic Findings with Those Specific to H. pylori-Eradicated Patients

Last, we summarized a comparison of general gastric cancer risk factors and characteristics with those specific to eradicated patients (Table 3). Most risk factors and characteristics overlap, but some are unique to eradicated patients. Regarding the risk factors of gastric cancer, pepsinogen levels change due to eradication, and map-like redness is unique to eradicated patients. Gastritis-like appearance, depressed type, and relatively small size are endoscopic findings that are characteristics of gastric cancer after eradication.

Conclusion

In this review article, we reviewed studies on the predictors of primary and metachronous gastric cancer after successful *H. pylori* eradication, characteristics of gastric cancer after eradication, and the usefulness of image-enhanced endoscopy for gastric cancer after eradication. We believe that efficient surveillance of high-risk patients can lead to early detection of gastric cancer in the era of *H. pylori* eradication.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have not received any funding for this review.

Author Contributions

Satoki Shichijo drafted the article. Noriya Uedo was responsible for critical revision and final approval of the article. Tomoki Michida provided final approval of the article.

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