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Short-term endoscopic alterations of early gastric cancer after successful eradication of Helicobacter pylori

Xiaohan Yan[1†], Jingze Li[1†], Zehua Zhang[1], Bensong Duan[1], Meidong Xu[1*] and Qinwei Xu[1*]

Abstract

Background Detecting and demarcating early gastric cancers (EGC) after eradication therapy of Helicobacter pylori (H. pylori) is a challenging task due to the fact that the lesion's surface is covered with gastritis-like tissue (non-neoplastic epithelium covering the cancerous tissue). However, our study aimed to investigate the endoscopic alterations of EGC within 3 months after eradication, which has not been reported clearly yet.

Methods Consecutive EGC patients who underwent two gastroscopies (one with H. pylori infection and another within 3 months after successful H. pylori eradication) were enrolled. The endoscopic photographs were evaluated for the endoscopic features and confidence level of demarcation line (DL), invasion depth, and histopathological classification by three highly experienced endoscopists. The DL estimated by endoscopy was compared with that of postoperative pathological examination.

Results 45 pairs of EGC cases before and after eradication were enrolled. All the confidence level of DL (High confidence: 15.6% vs. 93.3%, *p* value = 0.000) and invasion depth (High confidence: 37.8% vs. 80.0%, *p* value = 0.000) and histopathological classification (High confidence: 31.1% vs. 91.1%, *p* value = 0.000) were significantly improved after eradication. A higher confidence level of DL before eradication was correlated with severe atrophy score (*p* value = 0.036). The inter-observer agreements for DL, invasion depth, and histopathological classification were 0.85 and 0.75 and 0.78, respectively.

Conclusions DL of EGC becomes much more apparent after eradication in the short-term. Eradication therapy is necessary even shortly prior to the procedure of endoscopic submucosal dissection (ESD) to help precise pre-procedure diagnosis and avoid incomplete resection.

Keywords Early gastric cancer, Eradication of Helicobacter pylori, Demarcation line, Narrow band imaging, Endoscopic submucosal dissection

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Introduction

Globally, gastric cancer (GC) is the fifth most commonly diagnosed cancer and the fourth leading cause of cancer-related death with over 1 million new cases and an estimated 769,000 deaths in 2020 and remarkably higher incidence rates in Eastern Asia [1]. Helicobacter pylori (H. pylori) has been designated as a definite carcinogen in gastric cancer by World Health Organization since 1994 [2].

Since endoscopic submucosal dissection (ESD) has generally been adopted as a therapeutic strategy for early gastric cancer (EGC), improving preoperative endoscopic diagnostic ability is essential for radical resection [3]. Furthermore, endoscopic morphology is influenced directly by eradication therapy, which affects the diagnostic accuracy of gastric cancer.

Inflammatory cell infiltration turned out to be a cause of misdiagnosis, suggesting that resolution of inflammation aid in the accurate diagnosis of EGC. Thus, eradication of H. pylori, as a major cause of inflammation, may improve the detection and qualitative diagnosis of EGC and endoscopic demarcation [4]. Although several reports indicate that H. pylori eradication in patients with EGC makes it challenging to detect lesions and determine their demarcate line [5, 6], because (i) the lesions become a smaller and flattened form after eradication; (ii) the lesions tend to have gastritis-like mucosal pattern due to non-neoplastic epithelium covering the cancerous tissue [3, 7–9]. However, these studies focused on EGC more than 6 months or 1 year after eradication neglect the endoscopic alterations that may occur within the first three months after eradication. In the present research, we aimed to explore the endoscopic alterations of EGC within 3 months after eradication. Furthermore, inflammation was reported to be significantly reduced four weeks after eradication [10]. Therefore, in order to clarify when eradication becomes effective, we divided patients into the following subgroups for comparison: patients who underwent the ESD procedure within one month after eradication, and those who underwent the procedure within two to three months after eradication.

Methods

Patients and study design

Consecutive patients with EGC who underwent one esophago-gastro-duodenoscopy (EGD) with the infection of H. pylori and another EGD within 3 months after successful H. pylori eradication in our centers between December 2019 and December 2022 were retrospectively enrolled. In the immediate aftermath of the detection of EGC with H. pylori infection, eradication therapy was begun. The latter EGD was performed as preoperative endoscopy or during the procedure of ESD. Infection of H. pylori was confirmed by at least one of the following reliable clinical tests: (a) ^{13}C-urea breath test; (b) rapid urease test; (c) histopathologic evaluation. Successful eradication of H. pylori was diagnosed by histopathologic evaluation during ESD or ^{13}C-urea breath test at least 1–2 months after eradication.

The exclusion criteria were as follows: (a) patients did not undergo ESD or surgery in our hospital; (b) patients with remnant stomach; (c) patients detected by EGD as advanced gastric cancers; (d) accurate observation of the endoscopic features was impossible because of a restless or agitated condition without sedation or adequate preparation for EGD. Eligible patients were divided into two subgroups: patients underwent ESD within 1 month after eradication, and those who underwent the procedure within 2–3 months after eradication.

Written informed consent for research use of the lesion images and histopathological specimens after deletion of any identifying data was obtained from all patients before enrollment. The study protocol was approved by the institutional ethics committee of Shanghai East Hospital (2021201), and it was performed in accordance with the Declaration of Helsinki and its subsequent amendments.

Endoscopic procedure

The narrow-band imaging and magnified endoscopies (GIF-H260Z, Olympus Medical Systems, Tokyo, Japan) were used in this study. Before the examination, dimethylpolysiloxane and pronase were given and intravenous anesthesia was performed. At least 80 clear pictures were taken in each patient, including the antegrade or retroflex views of each part of the stomach, by white light imaging (WLI) and narrow-band imaging (NBI) and magnifying endoscopy with narrow-band imaging (ME-NBI). More details can be seen in our previous published article [6].

Participating endoscopists

Three highly experienced endoscopists (HEEs) accredited by the Chinese Gastroenterological Endoscopy Society with an experience of magnifying endoscopy with NBI (ME-NBI) > 500 cases retrospectively participated in the evaluation of the images. The endoscopic images of high quality were obtained, and they were randomly presented to each of the HEE who evaluated the images for the endoscopic features and confidence level of demarcation line (DL) and confidence level of invasion depth and confidence level of histopathological classification (differentiated or undifferentiated type) by the combination of WLI and NBI and ME-NBI. The HEE judged the alterations of endoscopic appearance independently, unaware of the clinical information including the evaluation of the eradication therapy. The endoscopists assigned high-confidence (HC) or low-confidence (LC) levels to their evaluations. If individual diagnostic interpretations differed, the three endoscopists discussed the case until consensus

was reached. We also assessed the inter-observer agreements between the endoscopists.

Histopathological assessment

After resected by ESD or surgery, the specimens were analyzed by pathologist of gastroenterology with 3 years or more of experience. The revised Vienna classification was used for the diagnosis and evaluation of gastric cancer [11]: Category 4 (mucosal high grade neoplasia including high grade adenoma/ dysplasia, carcinoma in situ, suspicious for invasive carcinoma and intramucosal carcinoma) was diagnosed as early gastric cancer in this study. In lesions of mixed histological types, it was recorded as the predominant histological type [12].

The DLs estimated by endoscopy were compared with the results of postoperative pathological examination (Fig. 1). A diagnosis was considered accurate when the entire DL were consistent with the results

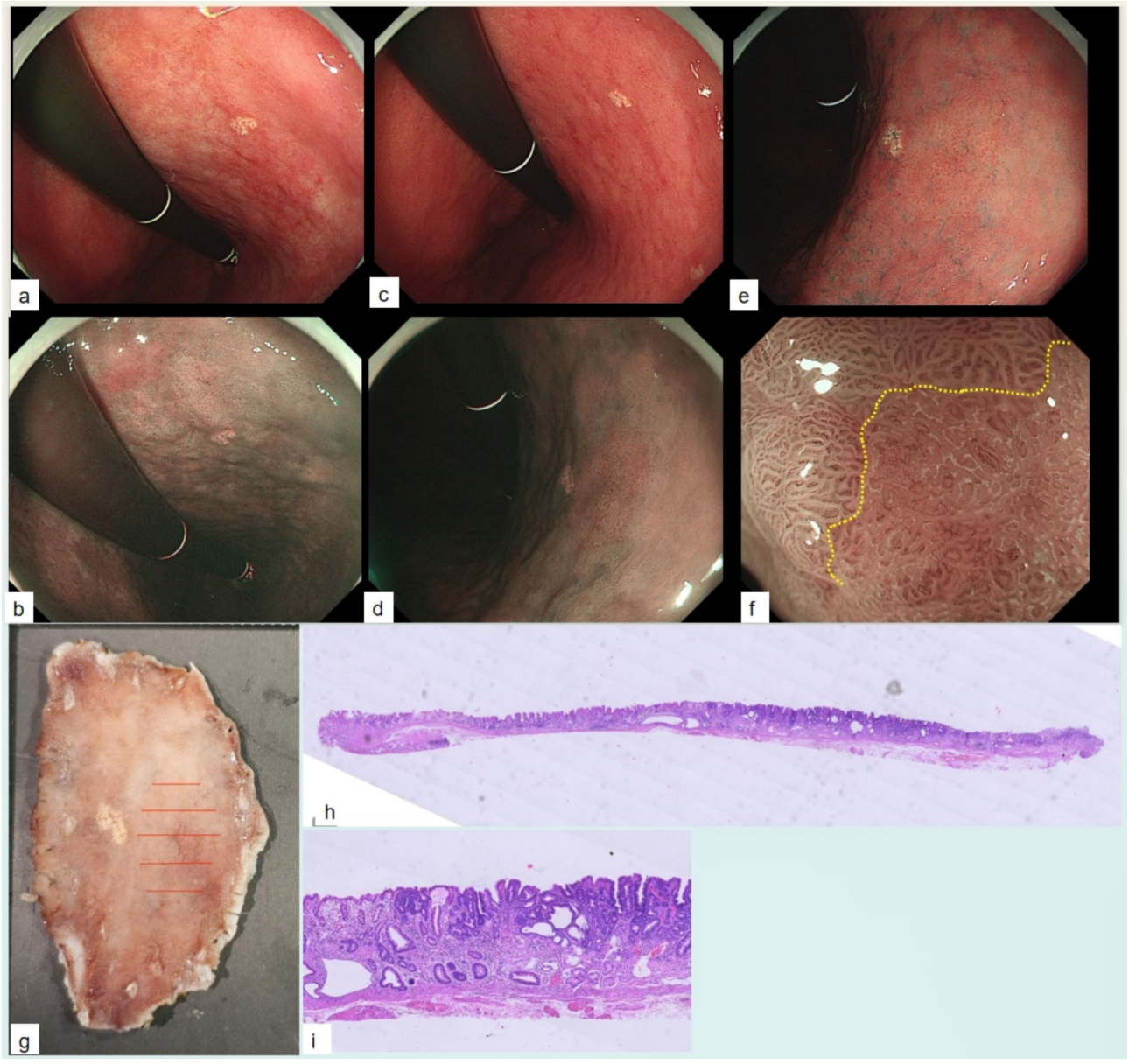

Fig. 1 The demarcation lines (DLs) estimated by white light imaging (WLI) and narrow-band imaging (NBI) were compared with the results of postoperative pathological examination. **a**, **b** The lesion of early gastric cancer (EGC) with H. pylori infection under WLI and NBI. **c**, **d**, **e**, **f** The same lesion three months after eradication therapy under WLI, NBI, dye-endoscopy, and magnifying endoscopy with narrow-band imaging (ME-NBI). The DLs became more distinct after eradication under NBI and ME-NBI. **g** Mapping of the lesion after endoscopic submucosal dissection (ESD). Gastric xanthoma was used as the oral side marking of the lesion. **h** Loupe view of a section. **i** Histopathological findings at the tumor border. 10×6 mm, high grade adenoma, M, UL (–), ly (–), v (–), HM0, VM0. DL, demarcation line; WLI, white light imaging; NBI, narrow-band imaging; EGC, early gastric cancer; ME-NBI, magnifying endoscopy with narrow-band imaging; ESD, endoscopic submucosal dissection

Table 1 The baseline characteristics of the early gastric cancer patients

	n **= 45**
Age (years)	64.1 ± 8.9
Male, n (%)	33 (73.3)
Tumor-occupied site, n (%)	
Upper region	8 (17.8)
Middle region	9 (20)
Lower region	28 (62.2)
Intermediate Zone	23 (51.1)
Depth of tumor invasion, n (%)	
Intramucosal	41 (91.1)
Submucosal (SM)	4 (8.9)
Complication, n (%)	
Hemorrhage	2 (4.4)
Perforation	0 (0)
Atrophy score (0: C-0, 1; 1: C-2, 3; 2:O-1, 2, 3)	1.31 ± 0.55
Histopathology, n(%)	
Differentiated	43 (95.6)
Well-differentiated tubular adenocarcinoma (tub1)	39 (86.7)
Moderately-differentiated tubular adenocarcinoma (tub2)	4 (8.9)
Undifferentiated	2 (4.4)
Signet-ring cell carcinoma (sig)	2 (4.4)
Curability, n (%)	
Complete (R0) resection	45 (100)
Incomplete resection (horizontal margin positive)	0 (0)
Lymphatic invasion (+), n(%)	0 (0)
Venous invasion (+), n(%)	0 (0)
Vertical margin (+), n(%)	0 (0)
Period after eradication therapy (months)	1.6 ± 0.4
Gastric xanthoma, n(%)	
Upper region	30 (66.7)
Middle region	11 (36.7)
Lower region	13 (43.3)
	6 (20)

of postoperative pathological examination. With the resected specimens cut into 2-mm slices, the acceptable error for accurate diagnosis was set at 1 mm or less.

Statistical analysis

Categorical variables were presented as absolute values and percentages, while continuous variables were expressed as the mean ± Standard deviation (SD). The differences between the groups were analyzed by the Chi-square test for categorical variables, and student-t test for continuous variables. The inter-observer agreements were measured by the kappa statistic. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 22.0 (IBM Corp. in Armonk, NY.)

Results

Patient characteristics

A total of 45 EGC patients were enrolled. The baseline characteristics are summarized in Table 1. The mean atrophy score was 1.31 ± 0.55. 51.1% of the lesions were located in the intermediate zone. In 30 (66.7%) cases, gastric xanthoma coexisted. The mean period after eradication therapy was 1.6 (0.5-3) months. The incidence of complications after ESD was low with 2 cases of hemorrhage and no perforation. Histopathological analysis showed that 41 (91.1%) EGC were located within the mucosal layer and 2 lesions invaded into the submucosal layer. 43 (95.6%) cases were differentiated type, while 2 (4.4%) were undifferentiated. All lesions achieved complete (R0) resection.

Table 2 Comparison of the endoscopic findings of the early gastric cancers before and after eradication therapy

	Before eradication	**After eradication**	***p*** **value**
Mean diameter of tumor (mm)	17.9 ± 8.8	16.2 ± 8.0	0.000
Macroscopic types, n (%)			0.326
Elevated	16 (35.6)	13 (28.9)	
Flattened/depressed	29 (64.4)	32 (71.1)	
Coloration under WLI, n (%)			
Red	40 (88.9)	20 (44.4)	0.000
Yellowish	3 (6.7)	23 (51.1)	0.000
Pale	2 (4.4)	2 (4.4)	1
Coloration under NBI, n (%)			
Brown	34 (75.6)	39 (86.7)	0.178
Green	9 (20.0)	4 (8.9)	0.134
Pale	2 (4.4)	2 (4.4)	1
Confidence level of DL, n (%)			0.000
Low confidence	38 (84.4)	3 (6.7)	
High confidence	7 (15.6)	42 (93.3)	
Confidence level of invasion depth, n (%)			0.000
Low confidence	28 (62.2)	9 (20.0)	
High confidence	17 (37.8)	36 (80.0)	
Confidence level of histopathological classification, n (%)			0.000
Low confidence	31 (68.9)	4 (8.9)	
High confidence	14 (31.1)	41 (91.1)	

WLI, white light imaging; NBI, narrow-band imaging; DL, Demarcation line

Endoscopic alteration of the same lesion prior to and following eradication therapy

As depicted in Table 2, the diameter of the tumor was significantly reduced from 17.9 ± 8.8 mm prior to eradication to 16.2 ± 8.0 mm after eradication (p value = 0.000). No significant differences were noted in macroscopic types (p value = 0.326) or coloration under NBI (p value = 0.178 and 0.134) between before and after eradication, statistically. Under WLI, the majority of lesions (88.9%) exhibited a red coloration before eradication, while the majority (51.1%) exhibited a yellowish coloration after eradication (p value = 0.000).

It is worth noting that the overall confidence level of DL (High confidence: 15.6% vs. 93.3%, p value = 0.000) and invasion depth (High confidence: 37.8% vs. 80.0%, p

value = 0.000) and histopathological classification (High confidence: 31.1% vs. 91.1%, p value = 0.000) significantly improved following eradication. As demonstrated in Figs. 2 and 3, the demarcation line became more apparent shortly after eradication, as the inflammation of the surrounding mucosa was effectively alleviated.

Furthermore, we found that a higher confidence level of DL prior to eradication was associated with a higher degree of atrophy (p value = 0.036). Moreover, the presence of gastric xanthoma was also correlated with a higher degree of atrophy (p value = 0.009), as depicted in Table 3.

Comparison of the confidence level in the subgroup analysis of the eradication time

Despite the significant elevation of the confidence level of DL, invasion depth, and histopathological classification after successful eradication within 3 months, we tried to clarify the difference between within 1 month and within 1–3 month after eradication. However, there was no substantial difference in the confidence level of DL (High confidence: 90.9% vs. 95.7%, p value = 0.524) and invasion depth (High confidence: 86.4% vs. 73.9%, p value = 0.297) and histopathological classification (High confidence: 95.5% vs. 87.0%, p value = 0.317) between the two eradication time subgroups, as evidenced in Tables 4 and 5.

Inter-observer agreements for the endoscopic evaluation of early gastric cancer

The inter-observer agreements with respect to DL, invasion depth, and histopathological classification were 0.85 (p value = 0.001) and 0.75 (p value = 0.014) and 0.78 (p value = 0.023), respectively, (Table 6). The inter-observer agreements were good-to-satisfactory.

Discussion

In the current study, we demonstrated the direct short-term effect of H. pylori eradication therapy on the morphological appearance in early gastric cancer, which is rarely explored and in growing demand. Previous research has reached consensus that the typical changes after eradication were (i) the appearance of normal columnar epithelium over the neoplastic lesion; (ii) a flattened or depressed aspect to the lesion and indistinct border of tumor lesion when viewed at endoscopy [3, 7–9]. However, the investigated lesions of these researches were EGC more than 6 months or 1 year after eradication. Although the surface epithelium over the tumor was found to be regenerative columnar epithelium (RCE) and epithelium with low-grade atypia (ELA) in some cases within 6 months [13], it is noted that the shortest duration after eradication in the EGC with a "gastritis-like" appearance was 6 months in the case control study [7]. Therefore, it is surmised that it costs at least 6 months after eradication for the histological surface differentiation and the microstructure maturation under NBI-ME [7]. Moreover, EGC after Hp eradication was defined, in multiple studies, as a lesion detected by endoscopy 1 year or more after successful eradication [3]. As far as we know, there is only one existing study focused on the morphological changes in human gastric tumors after eradication therapy of H. pylori in a short-term follow-up [14]. It is reported that 33% of 33 lesions became indistinct 1 month after successful eradication, contributing

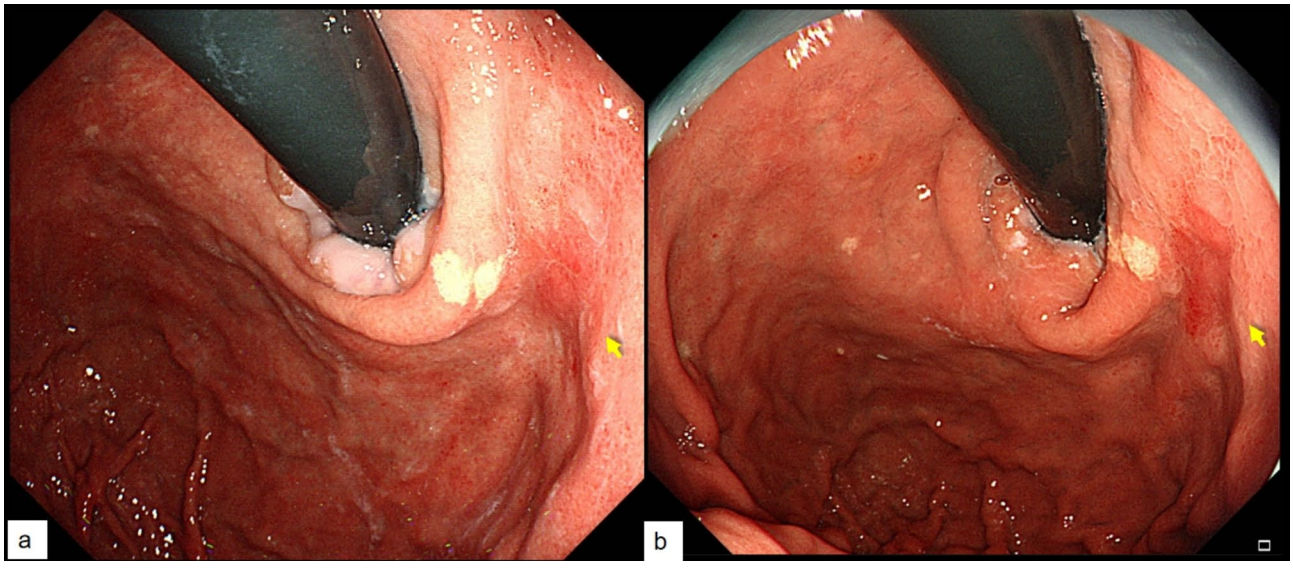

Fig. 2 The confidence level of demarcation line was significantly enhanced two weeks after the eradication therapy, as the inflammation of the surrounding mucosa was effectively reduced. The early gastric cancer was situated near a gastric xanthoma. **a** The lesion of early gastric cancer (EGC) with H. pylori infection under WLI. **b** The lesion of early gastric cancer (EGC) two weeks after eradication under WLI

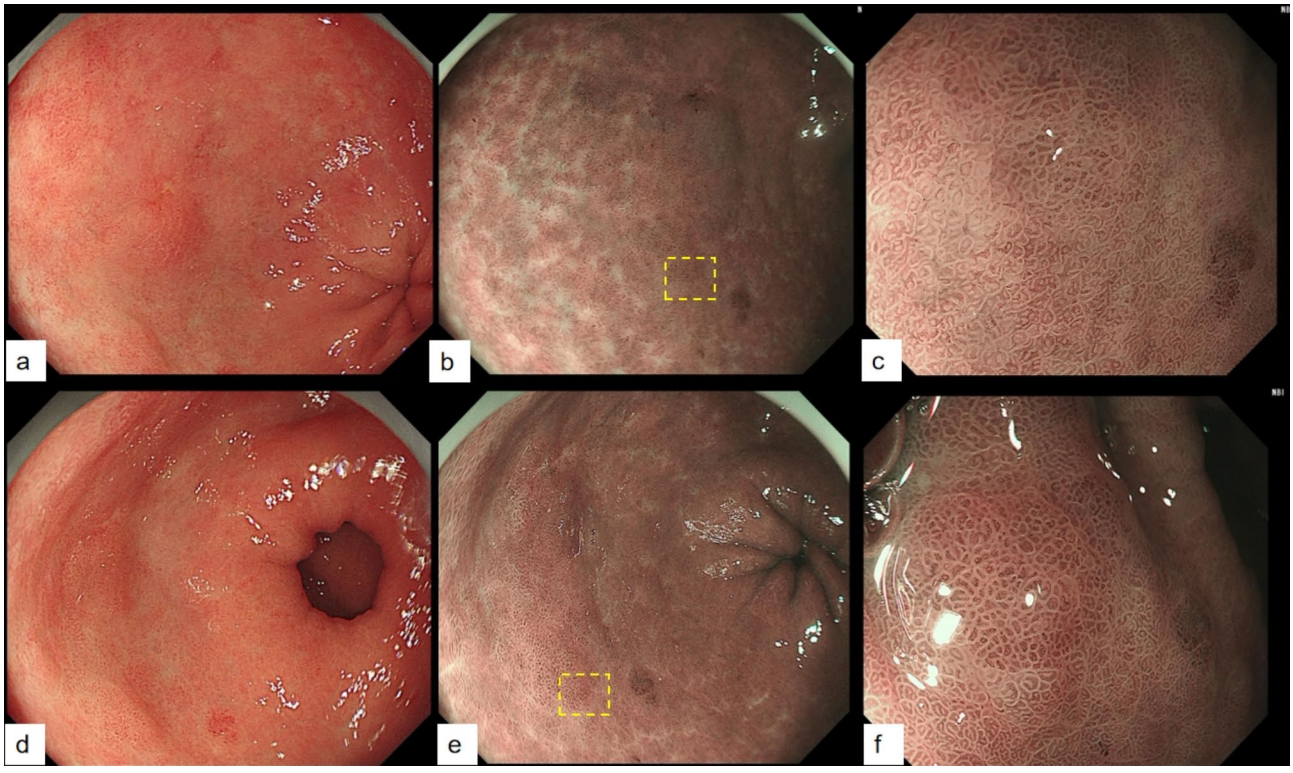

Fig. 3 The demarcation lines (DLs) became more apparent after eradication therapy due to reduced intervening parts (IP) in the surrounding noncancerous region estimated by white light imaging (WLI) and narrow-band imaging (NBI) and magnifying endoscopy with narrow-band imaging (ME-NBI). **a, b** The DLs of early gastric cancer (EGC) with H. pylori infection under WLI and NBI were indistinct. **c** The DL of EGC with H. pylori infection under ME-NBI was indistinct due to the extended IPs in the surrounding noncancerous region. **d, e** The DLs of the same lesion one week after successful eradication therapy became much more distinct under WLI and NBI. **f** The DL of the same lesion one week after eradication therapy was distinct under ME-NBI. The IPs caused by inflammatory cell infiltration were reduced in the noncancerous region. Thereby, the contrast between the IP in the cancerous region and the normal mucosa became apparent. DL, demarcation line; IP, intervening parts; WLI, white light imaging; NBI, narrow-band imaging; ME-NBI, magnifying endoscopy with narrow-band imaging; EGC, early gastric cancer

Table 3 The endoscopic findings of the gastric cancers in relate to the atrophy score

	Atrophy score	*P* value
Confidence level of DL before eradication, n (%)		0.036
Low confidence	1.23 ± 0.54	
High confidence	1.71 ± 0.48	
Gastric xanthoma		0.009
Present	1.47 ± 0.51	
Absent	1.00 ± 0.53	

DL, Demarcation line

Table 4 The baseline characteristics of the early gastric cancer patients after eradication therapy within one month and within 1–3 months

	≤ 1-month eradication group (*n* = 22)	> 1-month eradication group (*n* = 23)	*P* value
Age (years)	62.8 ± 9.8	65.3 ± 7.9	0.371
Male, n (%)	15 (68.2)	18 (78.3)	0.445
Tumor-occupied site, n (%)			
Upper region	5 (22.7)	3 (13.0)	0.396
Middle region	5 (22.7)	4 (17.4)	0.655
Lower region	12 (54.5)	16 (69.6)	0.299
Atrophy score (0: C-0, 1; 1: C-2, 3; 2:O-1, 2, 3)	1.23 ± 0.52	1.39 ± 0.57	0.329
Histopathology, n(%)			0.974
Differentiated	21 (95.5)	22 (95.7)	
Undifferentiated	1 (4.5)	1 (4.3)	

to the decreased tumor discovery rate [14]. Nevertheless, it was a study published in 2004 when the detection rate of EGC was quite low and NBI had not been applied in clinical use, thus resulting in different conclusions from our study.

It is first revealed by this study that the lesions became much more distinct and the DL was much clearer within 3 months after eradication on a global scale. To our knowledge, this is also the first research to compare the endoscopic features of the same lesions of the same patient before and after the eradication.

It is previously reported that the accuracy of diagnosis was higher when neutrophil and monocyte infiltration were mild according to the updated Sydney classification

Table 5 Comparison of the endoscopic confidence levels of the early gastric cancers after eradication therapy within one month and within 1–3 months

	≤ 1-month eradication group (*n* = 22)	> 1-month eradication group (*n* = 23)	*P* value
Confidence level of DL after eradication, n (%)			0.524
Low confidence	2 (9.1)	1 (4.3)	
High confidence	20 (90.9)	22 (95.7)	
Confidence level of invasion depth after eradication, n (%)			0.297
Low confidence	3 (13.6)	6 (26.1)	
High confidence	19 (86.4)	17 (73.9)	
Confidence level of histopathological classification after eradication, n (%)			0.317
Low confidence	1 (4.5)	3 (13.0)	
High confidence	21 (95.5)	20 (87.0)	

DL, Demarcation line

Table 6 Inter-observer agreements for the endoscopic evaluation of the early gastric cancer

Endoscopic evaluation of confidence level	Inter-observer agreement (kappa value)	*P* value
DL	0.85	0.001
invasion depth	0.75	0.014
histopathology	0.78	0.023

DL, Demarcation line

(USC) [15], and inflammatory cell infiltration renders diagnosis of demarcation line difficult. H. pylori eradication leads to resolution of inflammatory cell infiltration, which in turn reduces the extended intervening parts (IP) caused by inflammatory cell infiltration in the noncancerous region. Thereby, the contrast between the IP in the cancerous region and the normal mucosa becomes apparent [4, 16]. Although this phenomenon is primarily reported in cases of undifferentiated type [4, 16], we speculate that the pathophysiological changes are the same in differentiated cases. After eradication therapy, we found that IP had been markedly reduced in the surrounding noncancerous region (Fig. 3c and f). Thus, the contrast between the IP in the cancerous region and the normal mucosa became apparent, making the DL more distinct (Fig. 3). When inflammation is resolved, IP extended by cancer can easily be recognized under endoscopy. Consequently, it is much easier to determine the DL after the H. pylori eradication in a short-term, before the non-neoplastic epithelium, as a confounder factor, covers the cancerous tissue. Additionally, the brown hue resulting from inflammation under NBI diminishes in the surrounding mucosa post-eradication, accentuating the contrast between the cancerous region and the noncancerous mucosa. Moreover, the heterogeneity of micro-vessels improves and their average diameter decreases after eradication, subsequently increasing the confidence level of histopathological classification. The refinement of invasion depth confidence level after eradication may be attributed to alteration of non extension sign [17].

In the cases with infection of H. pylori (prior to eradication), high confidence level of DL has been shown to be related with severe gastric atrophy. In other words, DL are more apparent to be detected in cases with severe atrophy due to decreased inflammation in the local atrophy background. Gastric xanthoma has been identified as potential markers for predicting the development of EGC. In line with previous research, gastric xanthomas have been found to be associated with severe gastric atrophy [18, 19].

Differentiated-type cancers are often found to be small and macroscopically classified as the depressed type after H. pylori eradication [13, 20, 21]. During our research, we found several lesions of flattened type had turned into depressed type within 3 months. The duration after eradication was much longer in previous than in the present study. Thus, it is speculated that we could not find the statistical difference in the alteration of macroscopic types (*P* value = 0.326), because it may cost longer duration for the lesions to develop into depressed type, and because the lesions of both flattened type and depressed type were set as one group, compared with the elevated type group. The true pathogenesis of tumor flattering still remains unknown. Decreases in cytokine and serum gastrin levels in response to eradication therapy may be among the reasons of the inhibition of tumor growth and flattering of the tumor tissue [22, 23].

To evaluate the effects of the interval after H. pylori eradication, we compared the ≤ 1-month and > 1-month eradication subgroups. No significant difference was observed between the two subgroups in terms of the confidence level of DL and invasion depth and histopathological classification. On the basis of these findings, it can be assumed that, H. pylori eradication is suggested to aid the accurate diagnosis of EGC, even within one month.

Eradication therapy may cause some adverse effects like diarrhea and nausea and skin rash. In our opinion, eradication therapy is much more effective than administration of proton pump inhibitors (PPIs) or potassium-competitive acid blockers (PCABs) alone to eliminate inflammation according to our clinical experience, which is beyond the scope of this study. The DL of the patient after taking PPI for one month was still not clear, and the gastric mucosa was still heavily congested and oedematous (Fig. 2a). Only 2 weeks after eradication therapy, the inflammation gradually subsided and the DL became clear (Fig. 2b). However, further research is needed to explore this question.

This study has some limitations. First, this study investigated only cancerous lesions. A prospective study should be performed which enrolls lesions that have not undergone pathological diagnoses to avoid bias. Second, it was conducted at a tertiary endoscopy center with among the toppest EGC detection rate in China; hence, the data may lack generalizability to endoscopy centers worldwide. Third, it involved a review of endoscopic photos. Thus, it may not reflect the realtime diagnoses that occur during endoscopy. Fourth, it remains unclear whether tumor size in all cases was measured consistently with tools like calibrated forceps to ensure accuracy. This is due to the retrospective nature of the study. Thus, a margin of error of 1–2 mm could be expected, although we reported a significant reduction in tumor diameter after eradication therapy (17.9 ± 8.8 mm before eradication vs. 16.2 ± 8.0 mm after eradication, p value = 0.000).

In conclusion, the endoscopic characteristics undergo significant changes in the short term following eradication therapy. Our findings indicate that the DL of EGC lesions becomes more apparent after eradication therapy, which differs from previous reports. In cases where a suspicious lesion is detected, eradication therapy should be administered prior to ESD or surgery to facilitate an accurate pre-procedure diagnosis and prevent incomplete resection with positive horizontal margins.

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Author contributions
Meidong Xu and Qinwei Xu designed the study and reviewed the relevant literature. Xiaohan Yan and Jingze Li performed data analyses and wrote the manuscript for this study and contributed to the writing of the original draft. Zehua Zhang and Bensong Duan contributed to literature review. All authors have read and approved the final manuscript for submission.

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Data availability
The datasets used and/or analyzed during the current study can be obtained from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the institutional ethics committee of Shanghai East Hospital, and it was performed in accordance with the Declaration of Helsinki and its subsequent amendments. Informed consent was obtained from all the participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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