

## Reversal Phenomenon on the Mucosal Borderline Relates to Development of Gastric Cancer after Successful Eradication of *H. pylori*

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**Conflict-of-interest statement:** The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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**Received:** March 3, 2017

**Revised:** March 27, 2017

**Accepted:** March 28, 2017

**Published online:** April 21, 2017

### ABSTRACT

**AIM:** The characteristic endoscopic features of the gastric mucosa predictive of cancer development after successful eradication of *H. Pylori* have not been fully clarified. We have previously reported a reversal of red and white coloration in gastric corpus in some patients after eradication, and referred to it as the “reversal phenomenon on the mucosal borderline” (RP), which is often evident in patients who develop gastric cancer after eradication. Therefore we conducted a cross-sectional study to evaluate the correlation between RP and gastric cancer after *H. Pylori* eradication, and examined RP histologically.

**MATERIALS AND METHODS:** Patients with a history of successful eradication who underwent esophago-gastro-duodenoscopy (EGD) in our hospital between November 2015 and January 2016 were prospectively enrolled. The numbers of newly diagnosed cancers in RP-positive and negative groups were assessed. In addition, both red and white areas in the RP-positive patients were scrutinized by narrow-band imaging with magnifying endoscopy (NBI-ME), and histologically assessed by taking biopsy specimens.

**RESULTS:** Eighty-five patients were analyzed. Among them, 28 (32.9%) showed RP. Six cancers were found in the RP-positive group, and one in the RP-negative group ( $p < 0.01$ ). NBI-ME showed round pits without a light blue crest (LBC) in white areas, and round pits with LBC or villus-like structures with LBC or white opaque substance in red areas. All biopsy specimens from white areas had fundic glands, and all from red areas showed intestinal metaplasia.

**CONCLUSION:** Patients with RP tend to develop gastric cancer after eradication.

**Key words:** Gastric cancer, *H. Pylori*, Eradication therapy, Magnifying endoscopy, Narrow-band imaging

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Nawata Y, Yagi K, Tanaka M, Nakamura A. Reversal Phenomenon on the Mucosal Borderline Relates to Development of Gastric Cancer after Successful Eradication of *H. Pylori*. *Journal of Gastroenterology and Hepatology Research* 2017; **6(2)**: 2333-2338 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2021>

### INTRODUCTION

Gastric cancer can develop as a result of *Helicobacter pylori* infection<sup>[1]</sup>, and several reports have demonstrated that *H. Pylori* eradication reduces the incidence of gastric cancer<sup>[2,3]</sup>. Therefore, the health insurance system in Japan has approved eradication therapy for patients with *H. Pylori* gastritis. However, some patients develop gastric cancer even after successful eradication of *H. Pylori*.

A previous study found that gastric cancer changed to a flattened

and indistinct form after eradication, and that non-neoplastic epithelium covered the neoplasm in 73% of indistinct lesions<sup>[4]</sup>. We have also reported the characteristics of gastric cancer after *H. Pylori* eradication to be a gastritis-like mucosal pattern with an indistinct borderline by white light imaging and narrow-band imaging using magnifying endoscopy (NBI-ME), and that pathological examination demonstrates that the overlying non-neoplastic epithelium is mixed with cancerous ducts in a mosaic-like pattern<sup>[5]</sup>.

In order to discover indistinct gastric cancer after successful *H. Pylori* eradication, it would be useful to define the features of the gastric mucosa in which gastric cancers tend to develop after eradication. Previous studies have revealed that the risk factors for development of cancer after eradication include severe mucosal atrophy in the corpus<sup>[6]</sup>, emergence of map-like redness<sup>[7]</sup>, and histologically evident intestinal metaplasia (IM) or severe atrophy revealed by endoscopy<sup>[8]</sup>.

In Japan, the Kimura-Takemoto classification<sup>[9]</sup> has been widely used for many years. This is based on the fact that the atrophic side with pyloric glands in the lesser curvature of the corpus appears yellowish pale in color with visible capillary network whereas fundic side with superficial gastritis in the greater curvature appears homogeneously reddish before *H. Pylori* eradication.

On the other hand, while investigating characteristics of gastric cancer after *H. Pylori* eradication, we noticed atrophic side in the lesser curvature appeared red whereas fundic side in the greater curvature appeared white in some patients after *H. Pylori* eradication, in contrast to the appearance of conventional chronic active gastritis. We termed this finding “the reversal phenomenon on the mucosal borderline” (RP) (Figure 1), and revealed that RP had high specificity (93%) for the stomach after *H. Pylori* eradication<sup>[10]</sup>, and patients with gastric cancer after *H. Pylori* eradication often showed RP<sup>[11]</sup>.

To clarify the characteristic endoscopic features of the stomach after eradication where gastric cancer tends to develop, we evaluated the correlation between RP and gastric cancer after successful eradication of *H. Pylori*, scrutinized RP using NBI-ME, and examined RP histologically by taking biopsy specimens from both red and white areas in the present study.

## METHODS

### Study design and setting

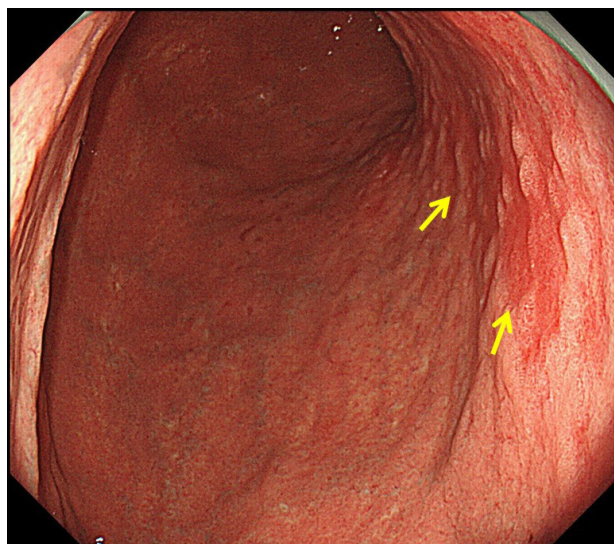
This was a cross-sectional study conducted at Niigata Prefectural Yoshida Hospital between November 2015 and January 2016. The study protocol was approved by our institutional ethics committee.

### Patients

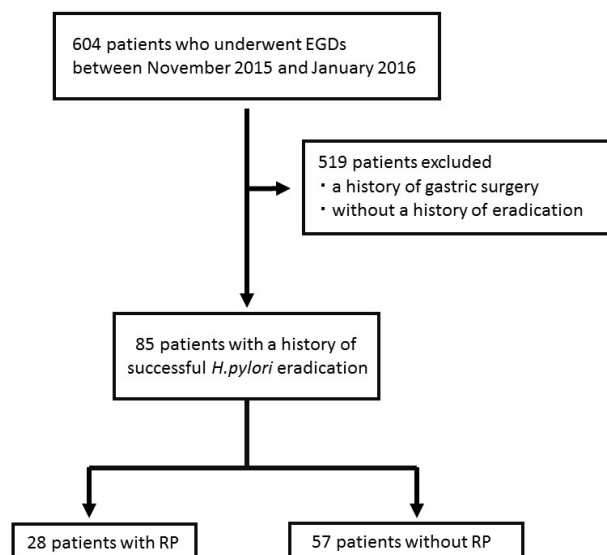
We prospectively enrolled patients with a history of successful *H. Pylori* eradication who underwent esophago-gastro-duodenoscopy (EGD) in our hospital during the study period. Successful eradication was confirmed by the <sup>13</sup>C-urea breath test (UBIT; Otsuka, Tokushima, Japan) and the *H. Pylori* stool antigen test (Premier Platinum HpSA; Meridian, Cincinnati, OH, USA), or by UBIT only. The exclusion criteria included a history of gastric surgery. Patients were divided into two groups according to whether RP was present or not. In both groups, we examined patient age, sex, period after eradication, reason for eradication and the number of newly diagnosed gastric cancers. Written informed consent was obtained from all patients before enrollment.

### Endoscopic procedures

The instruments used in the present study were a magnifying videoendoscope and an electronic endoscopic system (GIF H260Z,



**Figure 1** RP. RP revealed by conventional endoscopy in forward view. Yellow arrows indicate boundary between red and white areas. The red and white coloration is reversed in comparison with chronic active gastritis. RP, Reversal phenomenon on the mucosal borderline.



**Figure 2** Flow chart of patients. EGD, esophago-gastro-duodenoscopy. RP, Reversal phenomenon on the mucosal borderline.

GIF H290Z, and EVIS LUCERA ELITE; Olympus Medical Systems, Tokyo, Japan).

The EGD procedure used for examining the gastric corpus in this study was as follows. First we observed the whole gastric body using conventional endoscopy. Then, we identified endoscopically the atrophic border between the lesser and greater curvatures, which was recognized by discriminating differences in the color and height of the mucosa, as described previously by Kimura *et al* <sup>[9]</sup>. If the mucosa of the lesser curvature appeared white and that of the greater curvature appeared red, consistent with the Kimura-Takemoto classification, we judged the case to be RP negative. On the other hand, if the mucosa of the lesser curvature appeared red and that of the greater curvature appeared white, we judged the case to be RP positive, in contrast to the appearance of conventional chronic active gastritis.

If RP was recognized, we thoroughly observed the boundary between the red and white areas circumferentially for a width of several centimeters or more by conventional endoscopy and NBI-

**Table 1** Clinical data for patients in the two groups those with RP and those without.

	RP-positive (n=28)	RP-negative (n=57)	p value
Age, median (range)	69 (39-85)	70 (45-89)	0.47
Sex, female : male	5: 23	27: 30	< 0.01
Period after eradication (years) median (range)	4 (1-15)	3 (1-15)	0.67
Reason for eradication			
gastric cancer	7	14	
gastric ulcer	11	14	
duodenal ulcer	1	10	
gastritis	9	19	0.24
Newly diagnosed cancer	6	1	< 0.01

RP: Reversal Phenomenon on the mucosal borderline.

ME at lower magnification. We then obtained NBI-ME images of the red and white areas 1 cm distant from the boundary. Subsequently, if patients had given informed consent about taking biopsy specimens in advance, they were taken from both of the observed areas by NBI-ME.

In case lesions suspicious for gastric cancer were found, we took biopsy samples from there.

#### Histopathological assessment

The biopsy specimens were fixed in buffered formalin and embedded in paraffin. After hematoxylin and eosin staining, expert pathologist evaluated the specimens. The diagnosis of gastric cancer was based on the revised Vienna classification [12]: C4 (mucosal-high grade neoplasia) or C5 (submucosal invasion by carcinoma) was diagnosed as gastric cancer.

#### Statistical analysis

The clinicopathological data for the patients were analyzed by Mann-Whitney U test for numerical data and Fisher's exact probability test for categorical data. Differences at  $P < 0.05$  were considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

## RESULTS

A total of 604 patients underwent EGDs at our hospital during the study period. Among these patients, 85 had a history of successful *H. Pylori* eradication without a history of gastric surgery. Accordingly, these 85 patients were evaluated, and 28 (32.9%) of them showed RP (Figure 2). The clinical data for the patients in the RP-positive and negative groups are summarized in Table 1.

The number of male patients was larger in the RP-positive group than in the RP-negative group. The reasons for *H. Pylori* eradication were divided into four subgroups: gastric cancer (previously treated by endoscopic submucosal dissection; ESD), gastric ulcer, duodenal ulcer and *H. Pylori* -induced chronic active gastritis. No significant differences were found between the two groups in terms of age, period after eradication, and reason for eradication.

Six histologically proven gastric cancers were found in six patients in the RP-positive group (6/28; 21.4%), and one was found in the RP-negative group (1/57; 1.8%) ( $p < 0.01$ ) (Table 1). All of these newly diagnosed cancers were unrelated to the gastric cancers that had been previously treated by ESD, i.e., none were recurrent cancers. Six cancers were treated curatively by ESD, and one was treated by surgery because of massive submucosal invasion.

All of the 28 patients with RP showed the following NBI-ME findings. White areas demonstrated by conventional endoscopy were found to include round pits without a light blue crest (LBC), which indicates the presence of a fine, blue-white line on the crest of the epithelial surface/gyri, reportedly having a strong relationship to IM [13]. On the other hand, red areas demonstrated by conventional endoscopy were found to include round pits with a LBC or villus-like structures with a LBC. In some cases, the villus-like structures shown by NBI-ME were accompanied by a white opaque substance (WOS), which appears on part of the surface, and is reported to signify IM [14,15].

Biopsy specimens were taken from 6 patients who had given informed consent in advance. All of the biopsy specimens from white areas showed fundic glands without goblet cells, and all of those from red areas showed IM (Figure 3ABCDE).

## DISCUSSION

Although *H. Pylori* eradication has been thought to prevent gastric cancer development [2,3], gastric cancer has been found even after successful eradication. Furthermore, it has been reported that gastric cancer after eradication is difficult to detect and its lateral extent is unclear [4,5]. Therefore, there has been an urgent need to clarify the characteristic endoscopic features of the stomach after eradication where gastric cancer tends to develop.

In this study, we found that patients with RP are more likely to develop gastric cancer after *H. Pylori* eradication than those without RP. Previous studies have revealed that the risk factors for development of cancer after eradication include severe mucosal atrophy in the corpus [6], and histologically evident IM or severe endoscopic atrophy [8].

On the other hand, Moribata *et al.* have reported that emergence of map-like redness after eradication is a useful endoscopic feature for prediction of metachronous gastric cancer development after ESD [7].

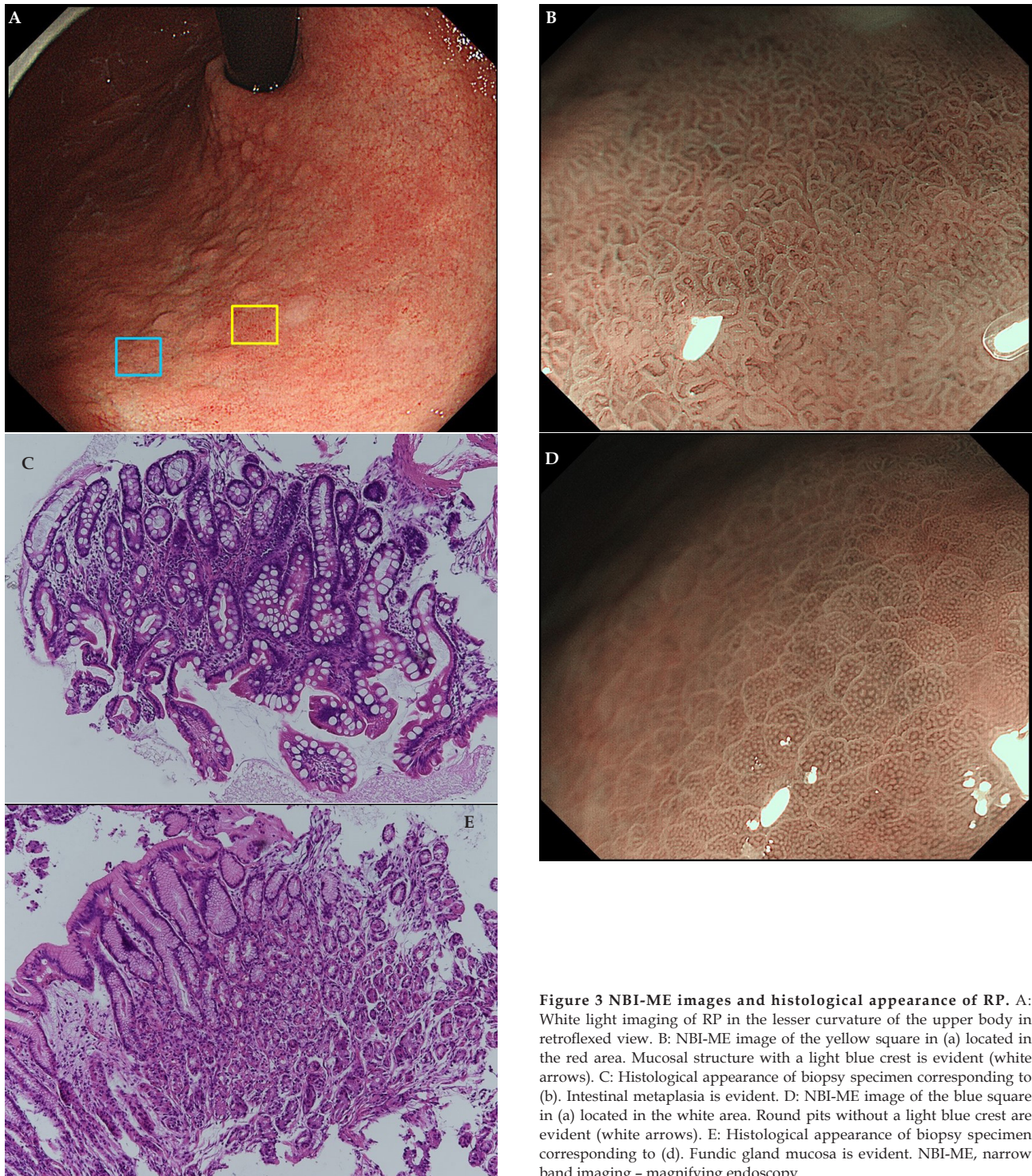
Map-like redness are synonymous with mottled patchy erythema (MPE), as reported by Nagata *et al.* [16], and considered to be a specific feature of the stomach after successful *H. Pylori* eradication [17]. After publication of the Kyoto classification of gastritis (in Japanese) [18] in 2014, MPE was renamed map-like redness.

The reversal phenomenon on the mucosal borderline, which we have advocated, denoted that the atrophic side on the lesser curvature of the corpus appeared red and the fundic side on the greater curvature of the corpus appeared white, in contrast to conventional chronic active gastritis based on the Kimura-Takemoto classification.

Although the red area in RP is thought to be map-like redness, we stress that the two conditions differ from each other in terms of location, and that the latter is independent of white areas and disappearance of gastric inflammation.

Nagata *et al.* defined MPE as flat or slightly depressed erythematous lesions under standard white light imaging endoscopy [16]. They presented pictures of MPE in the gastric antrum and angle. They reported that the IM percentages and median scores were both significantly higher in MPE areas than in non-MPE areas by taking biopsy samples from both MPE sites and surrounding non-MPE sites, however, they did not mention fundic glands at all.

On the other hand, in this study we revealed the histological and NBI-ME findings of RP. White areas demonstrated by conventional endoscopy were found to include round pits without a light blue crest (LBC), which were thought to be fundic glands [19], and histologically proved. Whereas red areas demonstrated by conventional endoscopy were found to include round pits with a LBC or villus-like structures with a LBC that were thought to be IM [13,20,21]. In some cases, villus-



**Figure 3 NBI-ME images and histological appearance of RP.** A: White light imaging of RP in the lesser curvature of the upper body in retroflexed view. B: NBI-ME image of the yellow square in (a) located in the red area. Mucosal structure with a light blue crest is evident (white arrows). C: Histological appearance of biopsy specimen corresponding to (b). Intestinal metaplasia is evident. D: NBI-ME image of the blue square in (a) located in the white area. Round pits without a light blue crest are evident (white arrows). E: Histological appearance of biopsy specimen corresponding to (d). Fundic gland mucosa is evident. NBI-ME, narrow band imaging – magnifying endoscopy.

like structures shown by NBI-ME were accompanied by a white opaque substance (WOS), which has been reported to indicate absorptive epithelium with an intestinal character<sup>[14,15]</sup>. In both areas the presence of IM were histologically proved.

The reason for the emergence of RP is thought to be disappearance of active inflammation including neutrophils in the fundic gland mucosa after *H. Pylori* eradication, leading to a change of color in fundic gland mucosa from red to whitish endoscopically<sup>[22]</sup>. However, the endoscopic appearance of intestinal metaplasia does not change after eradication. Consequently, areas of intestinal metaplasia are observed as red mucosa relative to fundic gland mucosa. Kiriya *et al.*<sup>[23]</sup> proved that eradication of *H. Pylori* alleviated hyperplastic

and hypertrophic enlargement of the foveolar epithelium only in gastric proper pyloric glands without IM, and not in glands with IM. This also supports our view that the color of IM does not change as a result of eradication.

In addition, most endoscopists in Japan usually use the Kimura-Takemoto classification in daily practice for judging the approximate extent of atrophic change. While observing many stomachs based on this classification, we have identified and reported a regular arrangement of collecting venules (RAC) characteristic of the *H. Pylori*-negative normal stomach<sup>[24]</sup>. Although it is well known that redness of the fundic gland mucosa disappears after *H. Pylori* eradication, we were the first to report reversal of that coloration<sup>[10]</sup>.

We think this process is reasonable for recognizing the disappearance of active inflammation, i.e. observing the atrophic border and identifying the presence of RP. The term RP is thought to be more appropriate than map-like redness in that mere expression of reddish area resembling a map does not represent the dynamic change in the whole stomach after *H. Pylori* eradication but rather localized redness. More accurately, RP might be better referred to as the reversal phenomenon of the Kimura-Takemoto classification. In order to facilitate dissemination of knowledge about the status of the stomach after eradication, we hope that the term RP will become widely known and used.

Our data indicated that male patients were more likely to show RP, possibly because more gastric cancers develop in men than in women. This might be because IM spreads in the lesser curvature of the corpus more extensively in male patients and tends to show RP, although further studies will be needed to confirm this. On the other hand, we found no significant differences in the reason for eradication between the two groups. That is to say, RP was observed irrespective of any previous history of endoscopic treatment for gastric cancer, which was thought to be a useful factor predictive of gastric cancer after eradication.

Among seven newly diagnosed gastric cancers, six were found in patients with RP and all of them were located in the corpus. Massive submucosal invasion was evident histologically in one case as a result of gastrectomy, which had not been evident 1 year previously. This lesion was located at the boundary between the red and white areas. We think that the spotted coloration and uneven mucosal surface around the boundary of RP tend to hinder recognition of cancer. Kobayashi *et al*<sup>[25]</sup> also reported that endoscopically mild or moderate atrophy in the background mucosa was associated with a tumor-obscuring gastritis-like appearance under NBI-ME after *H. Pylori* eradication. In fact, a considerable number of fundic glands were observed around the lesion in the surgical specimen, consistent with this notion. The gastritis-like appearance of that cancer might have hindered its recognition one year before.

The reason for the correlation between RP and the development of gastric cancer after *H. Pylori* eradication is not fully clear. Since the existence of fundic glands was proved, RP is inconsistent with severe endoscopic atrophy, which was previously indicated to be a high-risk factor. However, if the entire gastric mucosa is atrophic mucosa, it usually appears evenly flat and uniformly whitish, and thus detection of any lesion would not be difficult.

The present cross-sectional study was limited in that it was conducted at a single center and the sample size was small. In addition, identification of RP was somewhat subjective, and the endoscopists who screened the patients analyzed the data, therefore, this analysis had some selection bias. In this regard, a large-scale multicenter prospective study will be required to validate the usefulness of RP.

## CONCLUSION

RP was observed irrespective of any previous history of endoscopic treatment for gastric cancer. Gastric cancer tends to develop after successful *H. Pylori* eradication in patients with the reversal phenomenon on the mucosal borderline, which indicates the presence of both fundic glands and intestinal metaplasia. Careful examination is indispensable for finding gastric cancer after eradication.

## REFERENCES

1. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi

- S, Yamakido M, Taniyama K, Sasaki N, and Ronald J. Schlemper, *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297]; [DOI: 10.1056/NEJMoa001999]
2. Uemura N, Mukai T, Okamoto S, Yamaguchi S, Mashiba H, Taniyama K, Sasaki N, Haruma K, Sumii K and Kajiyama G. Effect of *Helicobacter pylori* eradication on subsequent development of cancer after endoscopic resection of early gastric cancer. *Cancer Epidemiol Biomarkers Prev* 1997 Aug; **6(8)**: 639-642. [PMID: 9264278]
3. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, Terao S, Amagai K, Hayashi S, Asaka M; Japan Gast Study Group. Effect of eradication of *Helicobacter pylori* on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008 Aug 2; **372(9636)**: 392-397. [PMID: 18675689]; [DOI: 10.1016/S0140-6736(08)61159-9]
4. Ito M, Tanaka S, Takata S, Oka S, Imagawa S, Ueda H, Egi Y, Kitadai Y, Yasui W, Yoshihara M, Haruma K, Chayama K. Morphological changes in human gastric tumours after eradication therapy of *Helicobacter pylori* in a short-term follow-up. *Aliment Pharmacol Ther* 2005 Mar 1; **21(5)**: 559-566. [PMID: 15740539]; [DOI: 10.1111/j.1365-2036.2005.02360.x]
5. Saka A, Yagi K, Nimura S. Endoscopic and histological features of gastric cancers after successful *Helicobacter pylori* eradication therapy. *Gastric Cancer* 2016 Apr; **19(2)**: 524-530. Epub 2015 Mar 10. [PMID: 25752268]; [DOI: 10.1007/s10120-015-0479-y]
6. Kodama M, Murakami K, Okimoto T, Abe H, Sato R, Ogawa R, Mizukami K, Shiota S, Nakagawa Y, Soma W, Arita T, Fujioaka T. Histological characteristics of gastric mucosa prior to *Helicobacter pylori* eradication may predict gastric cancer. *Scand J Gastroenterol* 2013 Nov; **48(11)**: 1249-1256. Epub 2013 Sep 30. [PMID: 24079881]; [DOI: 10.3109/00365521.2013.838994]
7. Moribata K, Iguchi JK, Nakachi K, Maeda Y, Shingaki N, Niwa T, Deguchi H, Inoue I, Maekita T, Tamai H, Ichinose M. Endoscopic features associated with development of metachronous gastric cancer in patients who underwent endoscopic resection followed by *Helicobacter pylori* eradication. *Dig Endosc* 2016; **28**: 434-442. [PMID: 26623565]; [DOI: 10.1111/den.12581]
8. Shichijo S, Hirata Y, Niikura R, Hayakawa Y, Yamada A, Ushiku T, Fukayama M, Koike K. Histologic intestinal metaplasia and endoscopic atrophy are predictors of gastric cancer development after *Helicobacter pylori* eradication. *Gastrointest Endosc* 2016 Mar 16. pii: S0016-5107(16)01053-1. [Epub ahead of print], [PMID: 26995689]; [DOI: 10.1016/j.gie.2016.03.791]
9. Kimura K, Takemoto T. An endoscopic recognition of the atrophic border and its significance in chronic gastritis. *Endoscopy* 1969; **1(3)**: 87-97. [DOI: 10.1055/s-0028-1098086]
10. Nawata Y, Yagi K, Tanaka M, Nakamura A, Saka A. Magnifying endoscopic findings of the gastric mucosa — gastritis, atrophy, and mucosa after eradication. *Stomach Intestine* 2016; **51(1)**: 52-63 (in Japanese).
11. Yagi K, Ajioka Y. Endoscopic diagnosis of gastric cancer after *Helicobacter pylori* eradication. Tokyo: Igakushoin; 2016 pp.5-11 (in Japanese).
12. Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. *Gut* 2002; **51**: 130-1. [PMID: 12077106]; [DOI: 10.1136/gut.51.1.130]
13. Uedo N, Ishihara R, Iishi H. A new method of diagnosing gastric intestinal metaplasia: narrow-band imaging with magnifying endoscopy. *Endoscopy* 2006 Aug; **38(8)**: 819-24. [PMID: 17001572]; [DOI: 10.1055/s-2006-944632]
14. Saka A, Yagi K, Nimura S. OLGA- and OLGIM-based staging of gastritis using narrow-band imaging magnifying endoscopy. *Dig Endosc* 2015 Nov; **27(7)**: 734-41. Epub 2015 Jun 8. [PMID: 25923666]; [DOI: 10.1111/den.12483]
15. Yao K, Iwashita A, Nambu M, Tanabe H, Nagahama T, Maki S,

- Ishikawa H, Matsui T, Enjoji M. Nature of white opaque substance in gastric epithelial neoplasia as visualized by magnifying endoscopy with narrow-band imaging. *Dig Endosc* 2012 Nov; **24(6)**: 419-425. Epub 2012 Apr 12. [PMID: 23078433]; [DOI: 10.1111/j.1443-1661.2012.01314.x]
16. Nagata N, Shimbo T, Akiyama J, Nakashima R, Kim HH, Yoshida T, Hoshimoto K, Uemura N Predictability of gastric intestinal metaplasia by mottled patchy erythema seen on endoscopy. *Gastroenterol Res* 2011; **4**: 203-209. [PMID: 27957016]; [PMCID: PMC5139844]; [DOI: 10.4021/gr357w]
  17. Watanabe K, Nagata N, Nakashima R, Furuhashi E, Shimbo T, Kobayakawa M, Sakurai T, Imbe K, Niikura R, Yokoi C, Akiyama J, Uemura N. Predictive findings for *Helicobacter pylori*-uninfected,-infected and -eradicated gastric mucosa: Validation study. *World J Gastroenterol* 2013 Jul 21; **19(27)**: 4374-4379. [PMID: 23885149]; [DOI: 10.3748/wjg.v19.i27.4374]
  18. Haruma K, Kato M, Inoue K, Murakami K, Kamada T. Kyoto classification of gastritis. 2014, Tokyo: Japan medical center (in Japanese).
  19. Yagi K, Honda H, Yang JM, Nakagawa S. Magnifying endoscopy in gastritis of the corpus. *Endoscopy* 2005 Jul; **37(7)**: 660-666. [PMID: 16010611]; [DOI: 10.1055/s-2005-861423]
  20. Yagi K, Mizuno, A, Nakamura A. Magnifying endoscopic findings of gastric mucosa, normal mucosa, gastritis, atrophy and mucosa after eradication. *Stomach Intestine* 2011; **46**: 841-852 (in Japanese).
  21. Kawamura M, Abe S, Oikawa K, Terai S, Saito M, Shibuya D, Kato K, Shimada T, Uedo N, Masuda T. Topographic differences in gastric micromucosal patterns observed by magnifying endoscopy with narrow band imaging. *J Gastroenterol Hepatol* 2011 Mar; **26(3)**: 477-483. [PMID: 21155881]; [DOI: 10.1111/j.1440-1746.2010.06527.x]
  22. Yagi K, Nakamura A, Sekine A. Magnifying endoscopy of the gastric body: a comparison of the findings before and after eradication of *Helicobacter pylori*. *Dig Endosc* 2002; **14(Suppl.)**: S76-S82. [DOI: 10.1046/j.1443-1661.14.s1.10.x]
  23. Kiriya Y, Tahara T, Shibata T, Okubo M, Nakagawa M, Okabe A, Ohmiya N, Kuroda M, Sugioka A, Ichinose M, Tatematsu M, Tsukamoto T. Gastric-and-intestinal mixed intestinal metaplasia is irreversible point with eradication of *Helicobacter pylori*. *Open Journal of Pathology*. Vol.6 No.2(2016), Paper ID 65663, 12 pages [DOI: 10.4236/ojpathology.2016.62012]
  24. Yagi K, Nakamura A, Sekine A. Characteristic endoscopic and magnified endoscopic findings in the normal stomach without *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 2002; **17**: 39-45. [PMID: 11895551]
  25. Kobayashi M, Hashimoto S, Mizuno K, Takeuchi M, Sato Y, Watanabe G, Ajioka Y, Azumi M, Akazawa K, Terai S. Therapeutic or spontaneous *Helicobacter pylori* eradication can obscure magnifying narrow-band imaging of gastric tumors. *Endoscopy* 2016; **04**: E665-672. Epub 2016 May 12. [PMID: 27556076]; [DOI: 10.1055/s-0042-105869]

Peer reviewer: Fan Xiaoming