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Clinical, Pathological and Endoscopic Features of Neoplastic or Non-neoplastic Reddish Depressed Lesions after *Helicobacter pylori* Eradication

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ABSTRACT

Background & Aims: Early gastric cancers (EGCs) after *Helicobacter pylori (H. pylori)* eradication often appear as reddish depressed lesions (RDLs); the same features are also appeared in benign stomachs after eradication. We compared clinic-pathological and endoscopic features of benign and neoplastic RDLs after *H. pylori* eradication.

Methods: 228 neoplastic RDLs after *H. pylori* eradication were studied. All lesions were divided into neoplastic RDLs (differentiated carcinoma or adenoma, n=114) and benign RDLs (n=114) according to the histology. Clinical and pathological characteristics were compared in neoplastic and benign groups. Endoscopic diagnostic yields using the white light (WL) endoscopy, chromoendoscopy (CE) using indigo carmine dye and the magnifying endoscopy with narrow-band imaging (ME-NBI) were also evaluated in relation to the pathological diagnosis.

Results: Size of neoplastic RDLs was larger than that of benign RDLs ($p<0.01$). Sensitivity, specificity and accuracy for predicting pathological types of RDLs was 70.1%, 52.6% and 61.4% for the WL, 65.8%, 63.1% and 65.4% for the CE, while the ME-NBI scored better with the 88.6%, 88.6%, 99.1% and 93.9% of sensitivity, specificity and accuracy. The accuracy of the ME-NBI was 99.9% (113/114) in the benign RDLs and 89.4% (101/114) for the neoplastic RDLs. Undiagnosed neoplastic RDLs using the ME-NBI were associated with more differentiated tumors such as adenoma and well-differentiated adenocarcinoma (tub1) and the presence of an unclear demarcation line.

Conclusions: ME-NBI is useful to diagnose RDLs after *H. pylori* eradiation, while some of neoplastic lesions are difficult to diagnose using the ME-NBI.

Key words: *Helicobacter pylori* – eradication – reddish depressed lesions – benign – neoplastic– magnifying narrow-band imaging endoscopy – conventional white light endoscopy – chromoendoscopy.

Abbreviations: CE: chromoendoscopy; DL: demarcation line; EGC: early gastric cancer; ER: endoscopic resection; *H. pylori: Helicobacter pylor*i; ME-NBI: magnifying endoscopy with narrow-band imaging; MV: microvascular; MS: microsurface; RDL: reddish depressed lesion; VS: vessel plus surface; WL: white light; WOS: white opaque substance.

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is the risk of gastric cancer [1, 2]; its infection causes chronic severe inflammation in the gastric mucosa which leads to the development of chronic atrophic gastritis and gastric neoplasia. A prospective study in Japan demonstrated that *H. pylori* eradication reduced the incidence of metachronous gastric cancer after endoscopic resection of early-stage gastric cancer (EGC) [3]. From 2013, the Japanese national health insurance system has covered the cost for eradication therapy for patients with *H. pylori* infection but have gastritis alone. Indeed, mortality from gastric cancer is now decreasing gradually with the increase rate of eradication therapy. However, gastric cancer is discovered in patients even after successful *H. pylori* eradication [4]. Early gastric cancer (EGC) found after *H. pylori* eradication sometimes appears with indistinct forms, such as tiny and flattened lesions [5-9]. These features may confuse endoscopic diagnosis. In cases with gastric adenoma, indistinct features after eradication was also reported [10].

Several studies had reported endoscopic features of EGC after *H. pylori* eradication as reddish depressed lesion (RDL)

[6, 8]. Although diffuse redness, a typical feature of H. pylori-infected gastritis [11], disappears after successful eradication, instead, cancer lesions are frequently appeared as RDLs. However, reddish lesions are also appeared as benign lesions called patchy redness and/or map-like redness [12, 13], which need to be distinguished from neoplastic lesion. Nagata et al. [13] reported that histological assessment of 55 patchy redness demonstrated that 87% (48/55) contained intestinal metaplasia in various degrees. Previous studies have demonstrated that magnifying endoscopy with narrow band imaging (ME-NBI), combined with conventional white light endoscopy (WL) can improve the diagnostic yield of EGC [14]. Kotachi et al. [15] reported that, compared to the RDLs diagnosed by the WL, RDLs diagnosed by the ME-NBI required fewer number of biopsies and obtained superior positive predictive value of biopsy to detect neoplastic lesions. However, it is unclear whether ME-NBI is effective in the diagnosis of EGC after *H. pylori* eradication [8, 9]. It is essential to clarify the clinical, pathological and endoscopic features of both benign and neoplastic RDLs after *H. pylori* eradication.

We investigated clinical and pathological features of both benign and neoplastic RDLs after *H. pylori* eradication. We also evaluated the diagnostic yields of different endoscopic modalities including WL endoscopy, chromoendoscopy (CE) using indigo carmine dye and ME-NBI to differentiate between benign and malignant RDLs.

METHODS

This was a retrospective study from single institution. We studied 228 neoplastic RDLs after *H. pylori* eradication. All lesions were divided into neoplastic RDLs (differentiated carcinoma or adenoma: 114 lesions from 84 patients) and benign RDLs (114 lesions from 99 patients) according to the histology by the endoscopic biopsy. 15 patients had multiple RDLs in the stomach including both benign and neoplastic RDLs. All patients attended the endoscopy center of Fujita Health University between April 2008 and March 2019. We defined the RDLs as localized reddish depression compared to the surrounding mucosa using conventional WL endoscopy. All lesions were diagnosed at least 6 months after successful *H. pylori* eradication for various reasons, including gastric ulcer or scarring and chronic gastritis, or after endoscopic resection (ER) of gastric neoplasia such as EGC and gastric adenoma. All RDLs were confirmed as either benign or neoplastic by the histological assessment of endoscopic biopsy. For all neoplastic RDLs, ER was performed, and all the lesions were confirmed as neoplastic by the histological assessment of ER specimens. For the benign neoplastic lesions, at least 6 month follow up endoscopy was performed and no evidence of malignancy was confirmed for the lesions. Fujita Health University School of Medicine approved the protocol of this retrospective study, and written informed consent was obtained from all participating subjects.

Clinical and pathological characteristics such as age, gender, post-eradication period, reason for eradication, were obtained from the medical records. Regarding the reason for *H. pylori* eradication, we classified the reason for eradication as follows; following ER of gastric neoplasia such as EGC or adenoma, gastritis, gastric ulcer (GU) and others. Based on the endoscopic images, atrophic gastritis in the corpus was classified according to the Kimura-Takemoto classification [16]. Size and anatomical location of the lesions were also investigated. Neoplastic RDLs were classified as adenoma or differentiated adenocarcinoma by the histological assessment of resected specimens. Differentiated adenocarcinoma was further divided into a well differentiated type (tub1) or moderately differentiated type (tub2). Submucosal invasion was also defined as SM1 (cases with submucosal invasion less than 500 μ and SM2 (cases with submucosal invasion greater than 500 μ) using the Japanese Classification of Gastric Carcinoma, 14th edition [17].

Endoscopic Procedure

Recorded endoscopic pictures were carefully evaluated by two experienced endoscopists (T.T. and N.H.). The video endoscope used in this study was an Olympus GIF-H260Z/H290Z (Olympus Medical Systems, Tokyo, Japan). All images of RDLs were evaluated first by WL followed by the CE and the ME-NBI in this order to diagnose the lesions as benign or neoplastic. We recorded all results immediately and did not change them even if a different diagnosis was made by other modalities. Diagnostic criteria of neoplastic RDLs by the WL and the CE was based on the presence of irregular findings, such as heterogeneous color, irregular demarcation or spiny depression, while no evidence of such findings was considered as a benign lesion. For the evaluation of ME-NBI pictures, we used vessel plus surface (VS) classification system [14]. In this system, endoscopic diagnosis of EGC is performed in terms of microvascular (MV), microsurface (MS) patterns and presence of demarcation line (DL). Diagnostic criteria of EGC was based on the presence of irregular MV and/or MS with DL. In addition, if the MS was relatively regular, but symmetrical distribution of the white opaque substance (WOS) or slit-like structures was observed, we diagnosed the lesion as gastric adenoma [18]. EGC and adenoma were considered as neoplastic lesions. No evidence of the above ME-NBI findings was considered as a non-cancerous lesion by the ME-NBI. All image interpretation was based on the consensus manner by two expert endoscopists (T.T. and N.H.) in order to evaluate their reasonability. If their opinions did not agree, a final judgment was arrived by consensus following the discussion of each individual case.

Statistical Analysis

Statistical differences of continuous variables between the two groups were determined using the Student‘s t-test. Categorical variables between the two groups were determined using the Chi-square Test. The Fisher‘s exact test was also used in case the cell frequency was equal to zero. Diagnostic yields of WL, CE and M-NBI were evaluated in terms of sensitivities, specificities, and diagnostic accuracies. All these parameters were calculated by reference to the pathological diagnosis. Differences at P values less than 0.05 were considered statistically significant.

RESULTS

Clinical and pathological characteristics among benign and neoplastic RDLs after *H. pylori* eradication are detailed in Table I.

Table I. Clinicopathological characteristics of benign and neoplastic RDLs

Variables	Benign RDLs (n=114)	Neoplastic RDLs (n=114)	p
Age, mean+/-SD	68.2±8.6	70.7±7.7	0.81
Gender, Male (%)	93 (81.6)	89 (78.1)	0.62
Post-eradication period: median months (range)	35.5 (6-209)	50 (6-341)	0.09
Reason for eradication, n(%):			
- following to ER	32 (28.6)	17 (16.0)	
- gastritis	52 (46.4)	43 (40.6)	0.01
- gastric ulcer	21 (18.8)	29 (27.4)	
-others	7 (6.2)	17 (16.0)	
Endoscopic atrophy: closed/opened (%)	38 (33.3) / 76 (66.7)	45 (39.5) / 69 (60.5)	0.41
Size: mean± SD mm	9.4±-5.3	13.0±10.3	<0.01
Location, n (%):			
- upper	16 (14.0)	24 (21.1)	
- middle	55 (48.2)	44 (38.6)	0.23
- lower	43 (37.7)	46 (40.3)	
Pathology: adenoma/tub1/tub2 (%)	-	3 (2.6) /81 (71.1) /30 (26.3)	-
Depth: M/SM1/SM2 (%)	-	93 (81.6) /8 (7.0) /13 (11.4)	-

Reason for eradication was unknown for 2 and 8 patients with non-neoplastic and neoplastic lesions, respectively; ER: endoscopic resection; tub1: well-differentiated adenocarcinoma; tub2: moderately-differentiated adenocarcinoma; SM1: cases with submucosal invasion less than 500 μm; SM2: cases with submucosal invasion greater than 500 μm.

Although age, gender, endoscopic atrophy, and anatomical location were not significantly different among those two groups, size of neoplastic RDLs was significantly larger than that of benign RDLs (p<0.01). We also found that specific reasons for eradication was different in those two groups (p=0.01). The cases who underwent eradication following ER seemed to be more frequent in benign RDLs (28.6% vs. 16.0%), on the other hand, cases who underwent eradication for other reasons seemed to be more frequent in neoplastic RDLs (6.2% vs. 16.0%). We also found that post-eradication period tended to be longer in neoplastic RDLs (35.5 months vs. 50 months, p=0.09).

Diagnostic yield of WL, CE and ME-NBI was evaluated in reference to pathological diagnosis. Representative endoscopic images of benign and neoplastic RDLs are shown in Fig. 1.

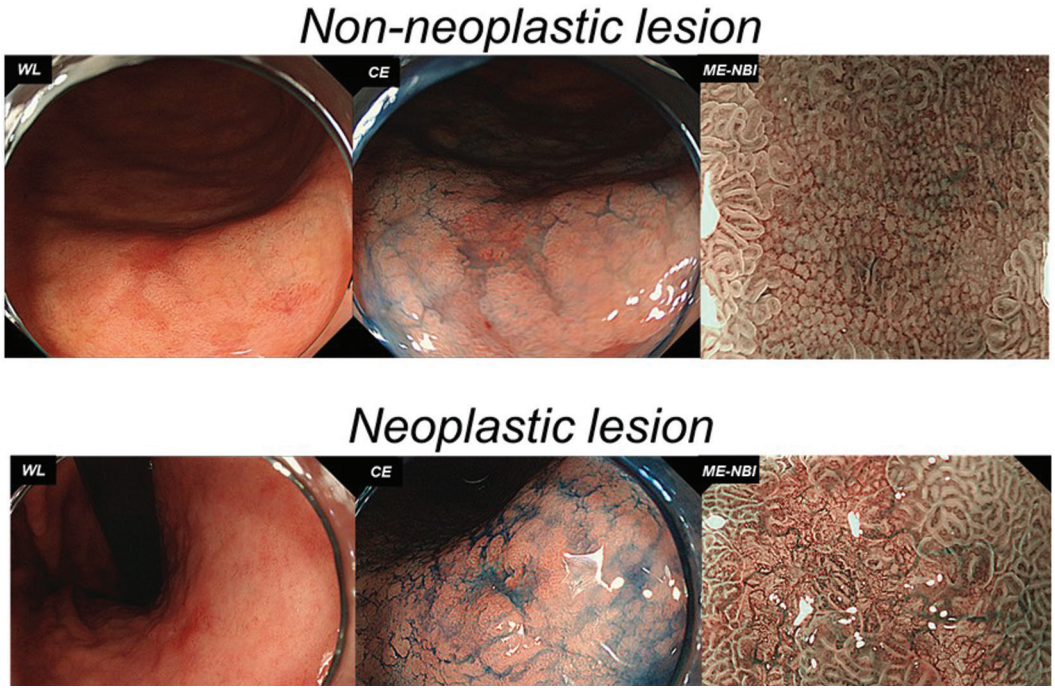

Fig. 1. Endoscopic images of benign (upper) and neoplastic (lower) RDLs after H. pylori eradication. Both lesions are appeared as 8mm sized RDL using WLE and CE. Using ME-NBI, irregular MV and clear DL were observed in the below lesion. In the upper lesion, MV and MS are uniform and clear DL is not observed. Pathological diagnosis of endoscopic biopsy was benign for the upper lesion and well-differentiated adenocarcinoma (tub1) for the below lesion, respectively.

Sensitivity, specificity and accuracy was 70.1%, 52.6% and 61.4% for the WL, 65.8%, 63.1% and 65.4% for the CE. On the other hand, sensitivity, specificity and accuracy was for the ME-NBI was 88.6%, 99.1% and 93.9%, which seemed to be superior to WL and CE (Table II). Next, we compared the diagnostic accuracy of the WL, CE, and the ME-NBI among benign and neoplastic RDLs (Table III). In both groups, diagnostic accuracy using WL and CE ranged from 52.6% to 70.2%. The accuracy for WL was higher in neoplastic group than in benign group (p<0.01). Diagnostic accuracy of the ME-NBI was 99.9% in the benign RDLs and 89.4% in the neoplastic RDLs. Notably, the accuracy for the benign RDLs was almost perfect, suggesting that ME-NBI can accurately confirm the benign RDL as a benign lesion. On the other hand, the accuracy for the ME-NBI was significantly lower in the neoplastic group than in benign group (p<0.01).

Table II. Diagnostic yields of WL, CE and ME-NBI in the diagnosis of RDLs after *H. pylori* eradication

Variables	Sensitivity	Specificity	Accuracy
WL	70.1%	52.6%	61.4%
CE	65.8%	63.1%	65.4%
ME-NBI	88.6%	99.1%	93.9%

WL: white-light; CE: chromoendoscopy; ME-NBI: magnifying endoscopy with norrow band imaging.

Undiagnosed Neoplastic RDLs by using the ME-NBI

The ME-NBI scored better for sensitivity, specificity and accuracy in comparison with the WL and the CE. But about 10% (13/114) of neoplastic RDLs seemed to be difficult to diagnose even using ME-NBI (Table III). A representative endoscopic and pathological finding of undiagnosed neoplastic RDL is shown in Fig. 2. We investigated whether specific clinic-pathological factors are associated with undiagnosed RDLs in the neoplastic group. Endoscopic atrophy, lesion size, location, histology, depth, and presence of demarcation line (DL) were included for the analysis (Table IV). The frequencies of histological types were significantly different among undiagnosed and diagnosed groups (p<0.01). Adenoma and well-differentiated adenocarcinoma (tub1) were more frequent in undiagnosed lesions than in diagnosed lesions (7.7% vs. 2.0% for adenoma, 92.3% vs. 62.4% for tub1, respectively). On the other hand, moderately-differentiated adenocarcinoma (tub2) was less frequent in undiagnosed lesions than in diagnosed lesions (0% vs. 36.6%). We also found that an unclear demarcation line (DL) according to the VS classification system was more frequent in undiagnosed lesions than in diagnosed lesions (92.3% vs. 29.7%, p<0.01). A trend was also found between undiagnosed lesions and smaller size (p=0.09). We also investigated the association between undiagnosed neoplastic RDLs and other factors such as age, gender, post-eradication period and reasons for eradication therapy, but no association was found for such factors (data not shown).

Table III. Diagnostic accuracy of WL, CE and ME-NBI among benign and neoplastic RDLs after H. pylori eradication

Variables	Benign RDLs (n=114)	Neoplastic RDLs (n=114)	p
WL	60/114 (52.6%)	80/114 (70.2%)	<0.01
CE	72/114 (63.2%)	77/113 (68.1%)	0.43
ME-NBI	113/114 (99.9%)	101/114 (89.4%)	<0.01

CE was not performed in one neoplastic lesion. For the abbreviations see Table II.

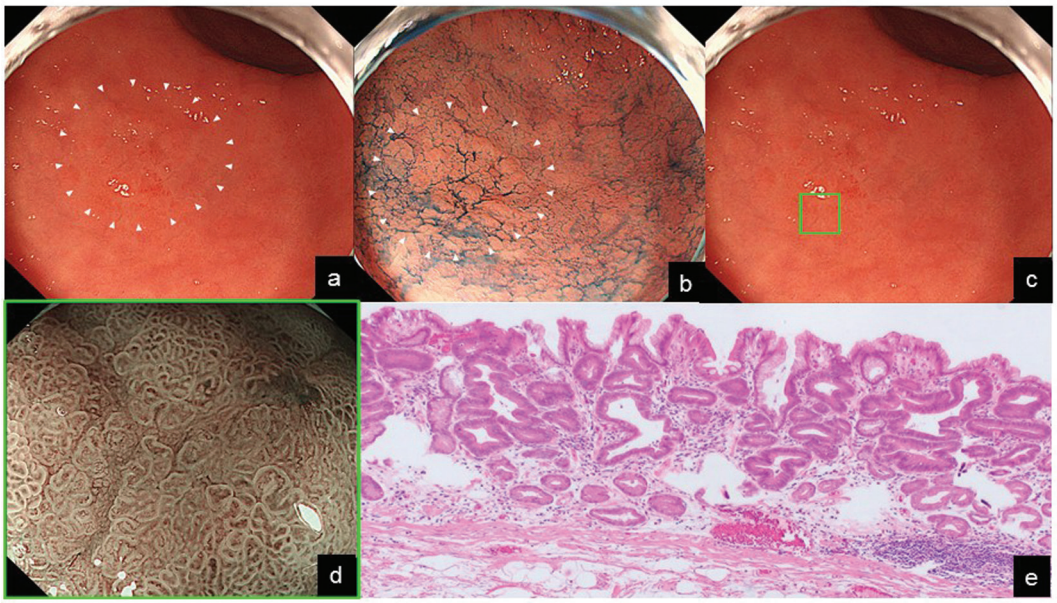

Fig. 2. Endoscopic and pathological findings of undiagnosed neoplastic RDL using ME-NBI. (a, b) A reddish depressed lesion was detected in the WL in the lower gastric body but the margin was unclear using CE (white arrow heads). (c, d) ME-NBI in the proximal area of this lesion showed some irregularity in the MS and MV patterns but the DL was unclear. (e) Histological examination of the resected specimen with Hematoxylin-Eosin staining showed non-tumoral epithelium covering over the well-differentiated adenocarcinoma (tub1).

Table IV. Clinic-pathological characteristics of diagnosed and undiagnosed neoplastic RDLs by using the ME-NBI

Variables	Diagnosed lesions (n=101)	Undiagnosed lesions (n=13)	p
Endoscopic atrophy: closed/opened (%)	40 (39.6) / 61 (60.4)	5 (38.5) / 8 (61.5)	0.94
Size: mean+/-SD mm	13.6+/-10.7	8.4+/-4.1	0.09
Location: U/M/L (%)	23 (22.8) / 40 (39.6) / 38 (37.6)	1 (7.7) /4 (30.8) / 8 (61.5)	0.21
Histology: adenoma/tub1/tub2* (%)	2 (2.0) / 62 (61.4) / 37 (36.6)	1 (7.7) /12 (92.3) / 0 (0)	<0.01
Depth: M-SM1/SM2 (%)	88 (87.3) / 13 (12.7)	13 (100) / 0 (0)	0.17
Demarcation line: clear/unclear (%)	71 (70.3) / 30 (29.7)	1 (7.7) / 12 (92.3)	<0.01

ER: endoscopic resection; GU: gastric ulcer; reason for eradication was unknown for 8 diagnosed lesions. tub1., well-differentiated adenocarcinoma; tub2, moderately-differentiated adenocarcinoma; SM1, cases with submucosal invasion less than 500 μm; SM2, cases with submucosal invasion greater than 500 μm; *: Frequency of tub2 was compared using the Fisher's exact test.

DISCUSSION

Although the histology of reddish lesions after *H. pylori* eradication might be mostly benign intestinal metaplasia [13], neoplastic lesions sometimes appear as RDLs [6, 8]. Therefore, specific clinic-pathological and endoscopic features of both benign and neoplastic RDLs need to be clarified. In the comparison of benign and neoplastic RDLs, neoplastic RDL was associated with larger size, while benign RDL was associated with specific reason for eradication such as following ER. Since the size of neoplastic RDLs was larger than that of benign RDLs, the larger RDLs need to be carefully diagnosed. On the other hand, regarding the reasons for *H. pylori* eradication, cases who underwent eradication following ER seemed to be more frequent in benign RDLs (28.6% vs. 16.0%). Generally, the patients who had a history of ER of EGC is a risk factor for metachronous gastric cancer [1, 3, 4]. Our data suggests that such patients are also likely to have benign RDLs, which confuses the precise detection of EGC lesions. As for other factors, we could not find any association between any clinical and pathological factors and histologic types of RDLs. Kotachi et al. [15] showed that male, open-type atrophy, and gastric cancer history were associated with presence of RDLs regardless of its histologic types, but all these are risk factors for gastric cancer following eradication therapy [19]. Therefore, it seems difficult to predict pathological types of RDLs by clinical and pathological factors alone.

To better understand endoscopic features of benign and neoplastic RDLs, we next investigated the diagnostic yield of RDLs by using WL, CE, and ME-NBI. The ME-NBI scored better for sensitivity, specificity and accuracy in comparison with the WL and the CE to predict the pathological types of RDLs. In particular, the accuracy for the ME-NBI was especially higher in the benign RDLs (113/114, 99.9%). Our result supports the diagnostic utility of ME-NBI for EGC in the previous study [14] and added the evidence that ME-NBI can accurately exclude the possibility of neoplasia in the benign RDLs after eradication. The diagnostic yields of ME-NBI including sensitivity (88.6%), specificity (99.1%) and accuracy (93.9%) seemed favorable, while the accuracy for the ME-NBI in the neoplastic RLDs was 89.4%, which was significantly lower than that of benign RDLs. This suggests that about 10% of neoplastic RDLs are difficult to diagnose even using ME-NBI.

We investigated clinic-pathological factors associated with undiagnosed RDLs in the neoplastic group. Undiagnosed neoplastic RDLs are associated with more differentiated histologic features such as well-differentiated adenocarcinoma (tub1) and adenoma. We have also found that the undiagnosed neoplastic RDLs are also associated with the presence of unclear DL. These results suggest that more differentiated tumors may be difficult to distinguish from surrounding benign mucosa. Therefore, such lesions are more likely to have unclear DL that makes endoscopic diagnosis difficult after eradication.

It is also reported that EGCs after *H. pylori* eradication often show distinct histological features such as regenerating non-tumorous epithelium covering over the tumorous tissue and/or surface differentiation of tumors, which also confuse endoscopic diagnosis [8, 9]. Such distinct histological findings may also be associated with unclear DL and diagnostic difficulty. Akazawa et al. [20] also reported that about 10% of EGCs after *H. pylori* eradication were difficult to demarcate from surrounding mucosa using the ME-NBI. In our study, unclear DL was observed in the majority of undiagnosed neoplastic RDLs (12/13, 92.3%) but it was also observed in about 30% (30/101) of the diagnosed group. A weak trend was also found between smaller size and undiagnosed neoplastic RDLs. It is possible that interaction of unclear DL and other factors such as smaller size is associated with diagnostic difficulty even using the ME-NBI, which needs to be further clarified.

Magnifying endoscopy with NBI provides accurate endoscopic diagnosis of gastric lesions with recent reports describing high accuracy and diagnostic efficacy in detecting EGC [14, 21]. The efficacy was also suggested in RLDs after *H. pylori* eradication with good positive predictive value of biopsy [15], but the study was limited to a few cases with endoscopic biopsy. We, therefore, thought that a larger number of both benign and neoplastic RDL lesions needed to be investigated to learn the specific endoscopic findings. One weakness of our study is its retrospective manner, which may lead to bias in case selection and image evaluation. However, in the clinical setting, only a few lesions would be neoplastic in the majority of RDLs. Detailed study on neoplastic RDLs may not be performed in the prospective design. One advantage our study has is the large number of lesions for which the pathological diagnosis was confirmed. Our result would be valuable to learn the

endoscopic features of both benign and neoplastic RDLs after *H. pylori* eradication.

CONCLUSIONS

Specific pathological types of RDLs are associated with their size and reason for eradication. The ME-NBI is useful to predict the pathological type of RDLs, while about 10% of neoplastic lesions are difficult to diagnose using ME-NBI. Further research is required to perform with a better design to evaluate our findings, which would help to establish diagnostic criteria of gastric cancer presenting with RDLs after successful *H. pylori* eradication.

Conflicts of interest: None to declare.

Authors' contribution: T.Tahara conceived and designed the study. N.H., H.Y., T.Terada, D.Y., M.O., K.F., Y.N., and T.S. collected and analysed the data. T.Tahara drafted the manuscript. N.O. supervised the study. All the authors revised the manuscript for its scientific content and approved the final version.

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