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約 120 名の参加があり、下記3. の契約形態見直しを事前に広く知らせることができた。また、治験依頼者側とセンター病院側の情報交換の機会にもなった。

3. コストの適正化のための契約形態の更なる見直し

「臨床研究・治験活性化5か年計画 2012 アクションプラン」に示されたコストの適正化に対応し、治験及び製造販売後臨床試験については、実施症例の出来高費用を更に分割し、進捗度により請求する方法とすることとした。センター病院の標準的業務手順書及び契約書等を一部改正し、平成 25 年 4 月 1 日から運用する。

G. 研究発表

1. 論文発表　該当なし
2. 学会発表　該当なし

H. 知的財産権の出願・登録状況

1. 特許取得　該当なし
2. 実用新案登録　該当なし
3. その他　該当なし

別紙４

研究成果の刊行に関する一覧表レイアウト（参考）

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著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

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Original Article

Changes in endoscopic findings of gastritis after cure of *H. pylori* infection: Multicenter prospective trial

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Background and Aim: Successful eradication of *H. pylori* changes pathological findings of gastritis dramatically. However, change of endoscopic mucosal findings is not fully understood. To clarify the short-term changes of endoscopic mucosal findings after cure of *H. pylori* infection, a multicenter prospective trial was conducted.

Methods: One hundred and forty-seven patients with *H. pylori* infection from 12 institutions were enrolled into this prospective cohort trial. Nineteen endoscopic findings using high-resolution white light electronic endoscopy were assessed before and 2–4 months after eradication treatment of *H. pylori*. *H. pylori* infection was diagnosed by pathology of three stomach sites using hematoxylin-eosin stain or *H. pylori*-specific immunostaining. Endoscopic features of the successful eradication group and the failed eradication group were compared. The change of severity of endoscopic features before and after *H. pylori* eradication were compared between successful eradication and failed eradication.

Results: One hundred and twenty-six patients were analyzed. Eradication rate was 81% (102/126). Non-transparency of gastric juice, diffuse redness of fundic mucosa, enlarged fold, spotty redness of fundic mucosa, flat erosion of stomach, and hemoglobin index of fundic mucosa were significantly different between the successful eradication group and the failed eradication group. Gastric flat erosion was of higher frequency in the successful eradication group. When eradication was successful, spotty redness of fundic gland improved significantly.

Conclusion: Assessment of endoscopic findings of spotty redness after eradication treatment is useful in the diagnosis of *H. pylori* eradication.

Key words: chronic gastritis, diffuse redness, endoscopic findings, erythema, *H. pylori* eradication

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INTRODUCTION

HELICOBACTER PYLORI INFECTS the human stomach for life and causes chronic inflammation of the gastric mucosa.[1] *H. pylori* infection induces infiltration of mononuclear cells and polynuclear cells into the gastric mucosa.[2] Atrophic change and intestinal metaplasia often occur during long-term persistent infection. *H. pylori* infection leads to a wide variety of upper gastrointestinal tract diseases, such as gastroduodenal ulcer, gastric adenocarcinoma, gastric mucosal-associated lymphoid tissue lymphoma, and gastric hyperplastic polyps.[3–7] Successful eradication of *H. pylori* improves histological gastritis and may prevent various diseases associated with *H. pylori* infection.[8]

It has long been believed that the features of conventional white light endoscopy correlate poorly with histopathological findings of *H. pylori*-induced gastritis.[9,10] Regular arrangement of collecting venules (RAC) was reported to be an endoscopic feature with high sensitivity and high specificity for the *H. pylori*-negative normal stomach.[11] Studies using magnifying endoscopy have shown that endoscopic features are associated with histopathological findings related to *H. pylori* infection.[12–14] Successful eradication of *H. pylori* dramatically changes the histopathological findings of gastritis. Recently, changes of magnifying endoscopic features with narrow band imaging (NBI) were investigated during *H. pylori* eradication.[15,16] However, change of conventional white light endoscopic features have not been clarified. A multicenter prospective trial was conducted to elucidate short-term changes of conventional white light endoscopic features after cure of *H. pylori* infection.

METHODS

Subjects

THIS MULTICENTER PROSPECTIVE trial comprised 12 institutions affiliated with the 'Study group for establishing endoscopic diagnosis of chronic gastritis' founded by the Japan Gastroenterological Endoscopy Society. This study group conducted other studies on the relationship between findings of white light endoscopy and histological findings. One hundred and forty-seven patients with *H. pylori* infection were initially enrolled from January 2009 to December 2009. Patients eligible for enrollment aged 20 years or older received eradication treatment of *H. pylori* infection. Exclusion criteria were histories of gastric surgery, gastrectomy, and eradication of *H. pylori*, treatment with non-steroidal anti-inflammatory drugs, antiplatelet agents, anticoagulants, steroids, antibiotics, and proton pump inhibitors within 4 weeks prior to entry, severe liver, renal, and cardiopulmonary dysfunctions, blood diseases including anemia, and a hemorrhagic tendency.

This study was approved by the Ethics Committee of each institution and carried out in conformity with the Declaration of Helsinki. All subjects gave written informed consent.

Procedures

Enrolled patients received high-resolution white light endoscopic examination to assess endoscopic findings before *H. pylori* eradication. *H. pylori* infection was diagnosed by rapid urease test upon initial endoscopic examination or by ^{13}C urea breath test prior to study. After the initial endoscopy, 10 mg rabeprazole, 200 mg clarithromycin, and 750 mg amoxicillin were given twice a day for 1 week, according to Japanese guidelines for management of *H. pylori* infection.[17] In patients with active gastric and duodenal ulcer disease, a proton pump inhibitor or a histamine receptor antagonist was given for 5 to 7 weeks after eradication therapy. A second endoscopic examination was carried out 2–4 months after eradication treatment and at least 4 weeks after completion of proton pump inhibitor treatment. Results of *H. pylori* eradication were diagnosed by pathological examination of three stomach sites during the second endoscopy. Diagnostic tools in which the result is known within a short time, such as the urea breath test, were excluded from this study in order to keep the endoscopist blinded to the eradication result. Biopsy samples were taken from one site each in the greater curvature of the antrum, the greater curvature of the upper body, and the lesser curvature of the angle. One specialized pathologist (H.W.) carried out blind assessment of *H. pylori* infection using hematoxylin-eosin (HE) staining or *H. pylori*-specific immunostaining. As immunostaining was added for distinguishing *H. pylori* from other microorganisms and also for detecting coccoid forms of *H. pylori*, the accuracy of histological diagnosis was expected to be the same as that of the urea breath test. Comparisons were made of the endoscopic features of successful and failed eradication groups and of the endoscopic features before and after successful eradication. End point was the diagnostic characteristics of endoscopic findings after successful eradication of *H. pylori*.

Endoscopic assessment

All endoscopists involved in the present study were accredited members of the Japan Gastroenterological Endoscopy Society. The high-resolution white light endoscope in this study was the GIF-240 series or the GIF-260 series (Olympus Medical Systems, Tokyo, Japan). Chromoendoscopy using 0.2% indigocarmine was carried out after the completion of conventional observation of the target region. Hemoglobin (Hb) index values of the fundic mucosa were carried out by institutions familiar with this method. Hb index

was measured using an image-processing system according to a previous report.[18] Two close-up pictures of the fundic mucosa without specific lesions, such as erosion and patchy redness, were obtained at the posterior wall of the upper gastric body. Characteristics of 10 endoscopic features were defined mainly based on endoscopic division of the Sydney System.[19] Another nine features, such as non-transparency of gastric juice, diffuse redness, RAC, adhesive mucus, xanthoma, fundic gland polyp, extent of atrophy, swelling of pyloric gland region with indigocarmine staining, and Hb index of fundic mucosa, were added to evaluate the endoscopic findings. The 19 features are described below.

1 Non-transparency of gastric juice: This is determined by visibility of gastric mucosa at the bottom of gastric juice. Severity increases as visibility decreases.
2 Diffuse redness of fundic mucosa: This refers to uniform redness involving the entire mucosa of the fundic gland. RAC is visible without diffuse redness.
3 Mucosal edema (fundic pyloric mucosa): This is characterized by soft, thick, and swollen gastric mucosa.
4 Enlarged fold: This constitutes fold enlargement. Normal fold is straight, smooth, and approximately 5 mm in diameter.
5 Visibility of vascular pattern: Atrophy is diagnosed by the visibility of the vascular pattern and rugal atrophy.
6 RAC: Starfish-like red spots in a regular arrangement are visible through the mucosal surface in the fundic gland region. Visibility of RAC is affected by inflammation and atrophy[11]
7 Nodularity: Nodular protrusions measuring 2–3 mm are uniformly distributed in the antrum and angle.
Severities of the qualitative findings from categories 1 to 7 listed above were divided into four grades: none (−), intermediate (+/−), clear (+), and remarkable (2+) (Fig. 1).
8 Adhesive mucus: Grayish or yellowish mucus adheres to the mucosal surface prior to washing with water.
9 Spotty redness of fundic mucosa: Multiple tiny reddish spots are observed in the fundic gland region. This finding should be strictly differentiated from patchy redness in the point of location, size and number. Typical spotty redness is defined as tiny reddish lesions < 1 mm in diameter that occur infinitely on the cardiac side of the fundic gland region.
10 Patchy redness (stomach duodenum): It is defined as localized reddish macula of various sizes. It occurs once or frequently, but it is isolated.
11 Red streaking: It is defined as reddish longitudinal streaks in the antrum and corpus.
12 Flat erosion (stomach duodenum): It is characterized by mucosal defects and whitish patches that vary in size.
13 Raised erosion: It is characterized as elevated mucosa with white excavation at the center.
14 Bleeding spot: It is defined as punctuated or ecchymotic reddish or brown- blackish flecks present in the gastric wall.
15 Xanthoma: It is characterized as yellow-white, well-demarcated, single or multiple nodules or plaques that vary in size.
16 Fundic gland polyp: It is characterized as tiny, numerous and sessile, usually scattered in the fundic gland region. They have the same color as the gastric mucosa. Severities of the quantitative findings from categories 8 to 16 listed above were divided into four grades: 0 (−), 1 (+−), 2–9 (+), and >10 (2+) (Fig. 2).
17 Extent of atrophy: The extent of atrophy was recorded according to the classification of Kimura and Takemoto.[20]
18 Swelling of areae gastricae in the pyloric gland region with indigocarmine staining: In the swollen areae gastricae, the inter-area groove is narrow. The classification was recorded according to Ida's paper.[21]
19 Hb index of fundic mucosa: Hb index is used as a parameter of the mucosal hemoglobin concentration and mucosal blood flow.[18] Calculated Hb index correlates value with the intensity of diffuse mucosal redness.

Statistical analysis

Statistical calculations were carried out with STATA ver. 11 software (StataCorp LP, College Station, TX, USA). The characteristics of eradicated subjects and failed subjects were compared by Wilcoxon signed-rank test, chi-squared test, or Student's *t*-test. Mann–Whitney rank-sum test or Student's *t*-test was used to assess the difference of endoscopic findings between the eradicated group and the failed group. Comparison of endoscopic findings before and after eradication in the two groups was analyzed using Wilcoxon signed-rank test. *P*-values <0.05 were considered to indicate statistical significance.

RESULTS

H. pylori eradication

ONE HUNDRED AND forty-seven patients with *H. pylori* infection were enrolled in the present study (Fig. 3). Seventeen patients were lost at the second endoscopic examination. Four patients were excluded for lack of histological specimens. Of the 126 patients in the final analysis, there were 69 with chronic gastritis, 20 with gastric ulcer scar, 12 with duodenal ulcer scar, 11 with active gastric ulcer, one with active duodenal ulcer, four after endoscopic resection of early gastric cancer, three with hyperplastic polyp, and six with miscellaneous diseases. The male-to-female ratio and mean age were 1.3 and 61.7 years, respec-

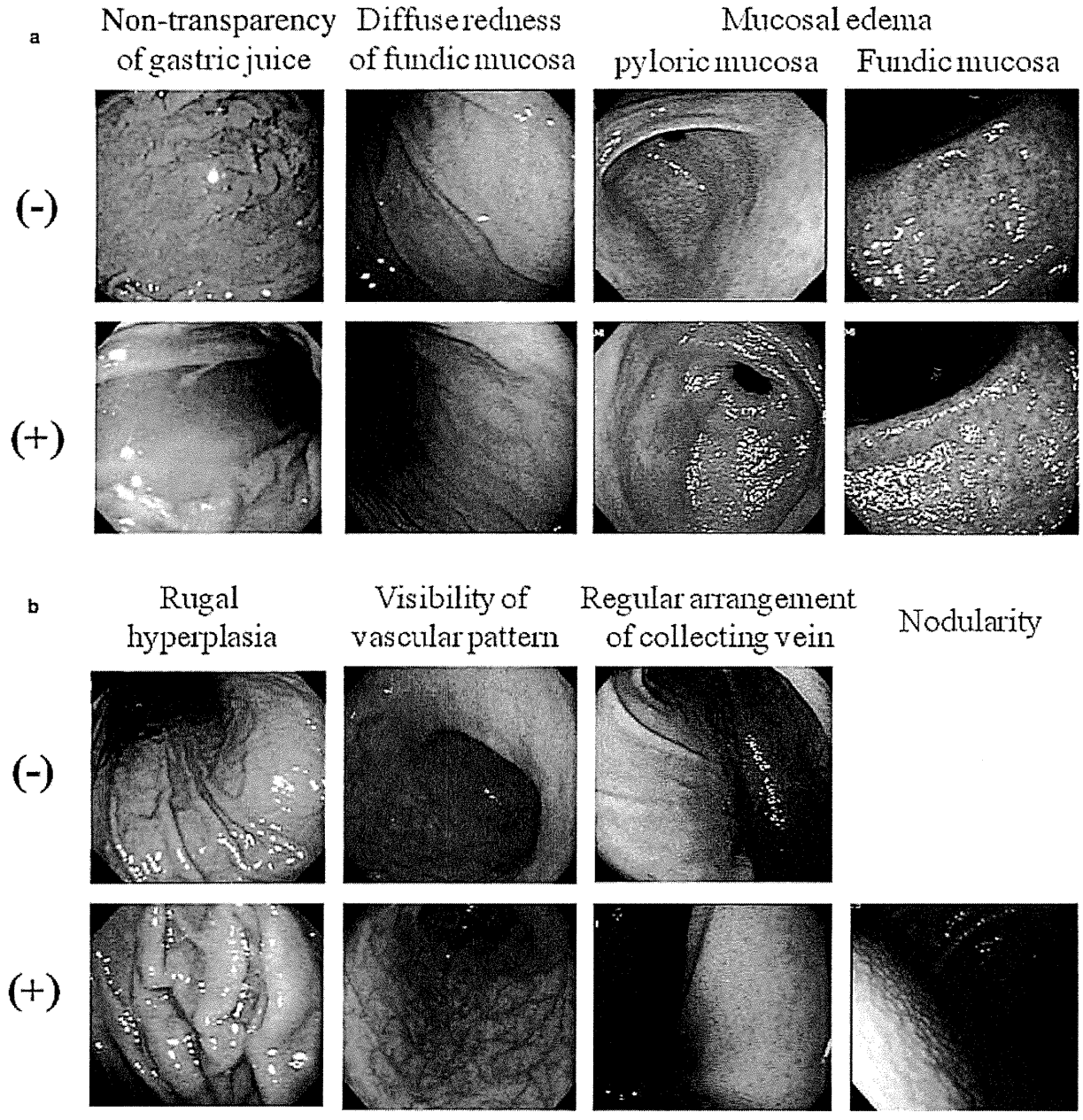

Figure 1 Grading of clear (+) and none (−) in the severity of seven qualitative findings.

tively. After eradication therapy of *H. pylori*, 102 patients were diagnosed with negative *H. pylori* infection using pathological examination and 24 patients were diagnosed with persistent *H. pylori* infection. Final eradication rate was 81% (102/126).

Comparison between successful and failed eradication group

Significant differences between the successful and failed eradication group were not seen in background characteris-

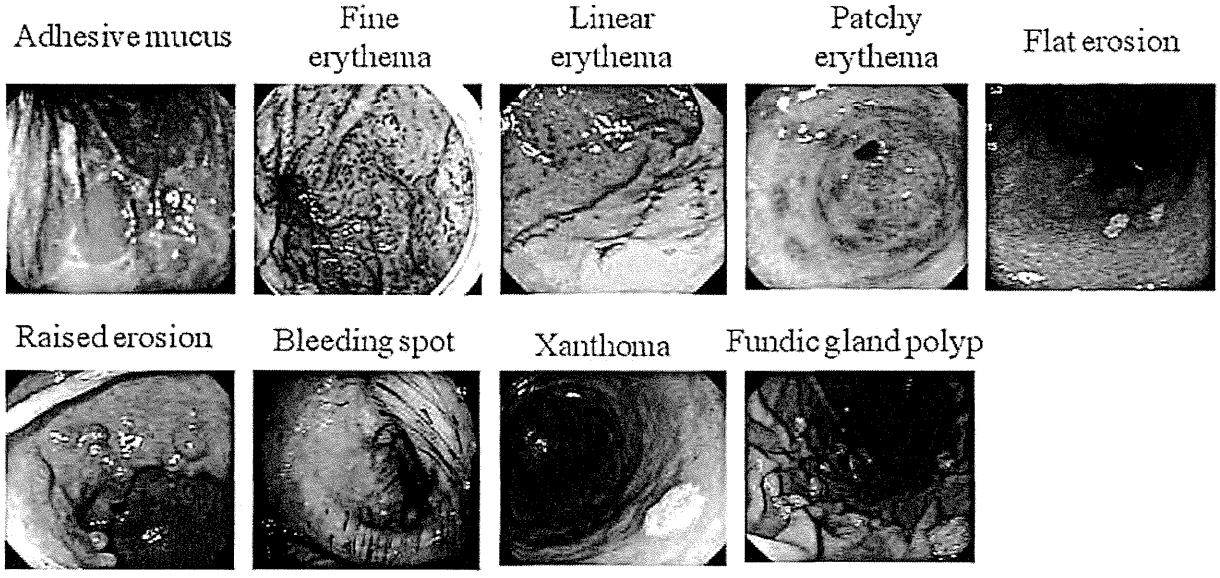

Figure 2 Nine quantitative findings.

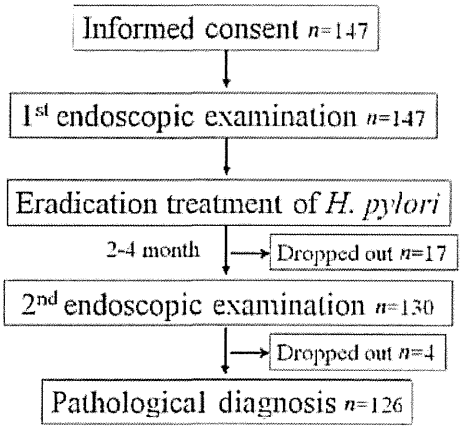

Figure 3 Protocol design.

ties such as age, sex, disease, and endoscopic findings, except diffuse redness of fundic mucosa. The successful eradication group had a lower grading in diffuse redness of the fundic mucosa than the failed group ($P = 0.0014$). Non-transparency of gastric juice, diffuse redness of fundic mucosa, enlarged fold, spotty redness of fundic mucosa, flat erosion of stomach, and Hb index of fundic mucosa after eradication were significantly different between the successful eradication group and the failed eradication group (Table 1). Other endoscopic findings had no significant differences (data not shown). Grading of endoscopic findings including diffuse redness, spotty redness, non-transparency of gastric juice, and enlarged fold were lower in the successful eradication group. Mean value of Hb index in the successful eradication group was lower than that in the failed eradication group. However, grading of gastric flat erosion was higher in frequency in the successful eradication group.

Comparison of change before and after *H. pylori* eradication between successful eradication and failed eradication

To evaluate specific endoscopic findings related to successful eradication and not to failed eradication, change of severity of endoscopic findings before and after *H. pylori* eradication were compared between successful eradication and failed eradication. Spotty redness of fundic mucosa was improved significantly in successful eradication cases compared with a small change in failed eradication cases (Table 2). Other significant endoscopic findings between the successful and failed eradication groups, in particular non-transparency of gastric juice, diffuse redness of fundic mucosa, enlarged fold, flat erosion of the stomach, and Hb index of fundic mucosa, did not show a significant difference because of an improvement in failed eradication cases (Table 3).

DISCUSSION

HELICOBACTER PYLORI INFECTION leads to various upper gastrointestinal tract diseases and influences gastric function, including gastric acid secretion. Successful

Table 1 Comparison between the failed and successful eradication groups

	Failed eradication (*n*)	(%)	Successful eradication (*n*)	(%)	*P* (rank-sum test if unspecified)
Non-transparency of gastric juice					
1	3	13.0	37	36.6	0.026
2	9	39.2	31	30.7	
3	8	34.8	30	29.7	
4	3	13.0	3	3.0	
Total	23	100.0	101	100.0	
Diffuse redness of fundic mucosa					
1	6	25.0	54	52.9	0.0093
2	9	37.5	30	29.4	
3	9	37.5	16	15.7	
4	0	0.0	2	2.0	
Total	24	100.0	102	100.0	
Enlarged fold					
1	4	16.7	31	30.7	0.038
2	5	20.8	29	28.7	
3	13	54.2	39	38.6	
4	2	8.3	2	2.0	
Total	24	100.0	101	100.0	
Spotty redness of fundic mucosa					
1	10	41.7	59	57.8	0.020
2	1	4.2	22	21.6	
3	11	45.8	19	18.6	
4	2	8.3	2	2.0	
Total	24	100.0	102	100.0	
Flat erosion of stomach					
1	22	91.7	72	70.5	0.035
2	0	0.0	2	2.0	
3	2	8.3	27	26.5	
4	0	0.0	1	1.0	
Total	24	100.0	102	100.0	
	Mean	SD	Mean	SD	
Hb index of fundic mucosa	62.4	4.6	57.8	5.7	0.030

Hb, hemoglobin.

Table 2 Change of spotty redness of fundic mucosa before and after *H. pylori* eradication between failed and successful eradication

	Failed eradication		Successful eradication		*P* (chi-squared test)
	(*n*)	(%)	(*n*)	(%)	
Spotty redness of fundic mucosa					
Non-improvement	19	79.2	56	54.9	0.029
Improvement	5	20.8	46	45.1	
Total	24	100.0	102	100.0	

eradication of *H. pylori* improves histological gastritis and may prevent various diseases associated with *H. pylori* infection, such as gastric/duodenal ulcer and gastric cancer.[22,23] Moreover, *H. pylori* eradication therapy is necessary to prevent the spread of this infection. The detection of *H. pylori* infection after eradication treatment is carried out using invasive and non-invasive tests such as pathological examination, culture, ^{13}C-urea breath test, and stool antigen test. The aim of

Table 3 Comparison of change before and after *H. pylori* eradication between failed and successful eradication

	Failed eradication		Successful eradication		*P* (chi-squared test or *Fisher's exact test)
	(*n*)	(%)	(*n*)	(%)	
Non-transparency of gastric juice					
Non-improvement	12	54.5	48	49.5	0.67
Improvement	10	45.5	49	50.5	
Total	22	100	97	100	
Diffuse redness of fundic mucosa					
Non-improvement	8	33.3	37	36.3	0.79
Improvement	16	66.7	65	63.7	
Total	24	100	102	100	
Mucosa edema of fundic mucosa					
Non-improvement	9	45.0	40	45.5	0.97
Improvement	11	55.0	48	54.5	
Total	20	100	88	100	
Mucosa edema of pyloric mucosa					
Non-improvement	8	40.0	36	42.4	0.85
Improvement	12	60.0	49	57.3	
Total	20	100	85	100	
Enlarged fold					
Non-improvement	16	66.67	48	48.98	0.12
Improvement	8	33.33	50	51.02	
Total	24	100	98	100	
Visibility of vascular pattern					
Non-improvement	19	79.2	81	79.4	0.98
Improvement	5	20.8	21	20.6	
Total	24	100	102	100	
Regular arrangement of collecting venules					
Non-improvement	23	95.8	90	89.1	0.46*
Improvement	1	4.2	11	10.9	
Total	24	100	101	100	
Nodularity					
Non-improvement	21	87.5	99	97.1	0.083*
Improvement	3	12.5	3	2.9	
Total	24	100	102	100	
Adhesive mucus					
Non-improvement	14	58.3	43	42.2	0.15
Improvement	10	41.7	59	57.8	
Total	24	100	102	100	
Patchy redness of stomach					
Non-improvement	20	83.3	79	77.5	0.53
Improvement	4	16.7	23	22.5	
Total	24	100	102	100	
Patchy redness of duodenum					
Non-improvement	23	95.8	94	94.0	1.00*
Improvement	1	4.2	6	6.0	
Total	24	100	100	100	
Red streaking					
Non-improvement	22	91.7	100	98.0	0.16*
Improvement	2	8.3	2	2.0	
Total	24	100	102	100	

Table 3 Comparison of change before and after *H. pylori* eradication between failed and successful eradication (continued)

	Failed eradication		Successful eradication		*P* (chi-squared test or *Fisher's exact test)
	(*n*)	(%)	(*n*)	(%)	
Flat erosion of stomach					
Non-aggravation	22	91.67	95	93.14	0.68*
Aggravation	2	8.33	7	6.86	
Total	24	100	102	100	
Raised erosion					
Non-improvement	23	95.8	99	97.1	0.58*
Improvement	1	4.2	3	2.9	
Total	24	100	102	100	
Bleeding spot					
Non-improvement	22	91.7	95	93.1	0.35*
Improvement	2	8.3	7	6.9	
Total	24	100	102	100	
Xanthoma					
Non-improvement	24	100.0	95	93.1	0.35*
Improvement	0	0.0	7	6.9	
Total	24	100	102	100	
Fundic gland polyp					
Non-improvement	23	95.8	102	100.0	0.19*
Improvement	1	4.2	0	0	
Total	24	100	102	100	
Extent of atrophy					
Non-improvement	22	91.7	84	82.4	0.36*
Improvement	2	8.3	18	17.6	
Total	24	100	102	100	
Swelling of areae gastricae					
Non-improvement	15	83.3	63	78.7	1.00*
Improvement	3	16.7	17	21.3	
Total	18	100	80	100	
Hb index of fundic mucosa					
Non-improvement	2	25	12	36.36	0.692
Improvement	6	75	21	63.64	
Total	8	100	33	100	

Hb, hemoglobin.

the present study was to evaluate endoscopic diagnosis for successful eradication of *H. pylori* infection. Endoscopy can improve the accuracy of diagnosis of *H. pylori* infection during examination without the need for biopsy. In this study, various kinds of white light endoscopic features were assessed before and after *H. pylori* eradication. Almost of these features were described in an endoscopic division of the Sydney System.[10] Other findings such as non-transparency of gastric juice, diffuse redness, RAC, adhesive mucus, xanthoma, fundic gland polyp, extent of atrophy, swelling of pyloric gland region with indigocarmine staining, and Hb index of fundic mucosa were reported to be associated with *H. pylori* infection.[11–14]

From our results, a decrease in spotty redness after eradication treatment was a significantly useful endoscopic finding for the diagnosis of successful eradication. Comparison between the successful and failed eradication groups showed a significant difference in six endoscopic findings. However, five endoscopic findings such as diffuse redness of fundic mucosa, non-transparency of gastric juice, enlarged fold, flat erosion of stomach, and Hb index of fundic mucosa were not specific changes in cases of successful eradication. These endoscopic findings could possibly be associated with temporary inhibition of gastric inflammation by suppression of *H. pylori*. Spotty redness of the fundic gland region is strictly influenced by curing *H. pylori* infection. As the

disappearance of polymorphonucleocytes is a histologically significant change shortly after *H. pylori* eradication, spotty redness of the fundic gland region is suggested to be related to histological activity.

Flat erosion of stomach and duodenum is related to recovery of acid output after successful eradication.[24] Basal gastric acidity increases after successful *H. pylori* eradication, but does not change for subjects with persistent infection.[25] Specifically, Japanese patients have a high likelihood of acid recovery after successful eradication because approximately 80% of *H. pylori* infected patients end up with corpus-predominant gastritis. Although an increase in duodenal erosion is due to acid recovery, it occurs less frequently and only for a short duration after successful eradication.

The change in conventional endoscopic features with white light imaging has not been clarified. However, the change in magnifying endoscopic features with narrow band imaging during *H. pylori* eradication has been reported. Yagi *et al.* evaluated magnifying endoscopic change focusing on mucosal and microvascular patterns 1 year after successful eradication.[15] Changes in magnified findings after successful eradication included disappearance of erythema and swelling of areas between gastric pits, pinhole-like changing of white pits, and recovery of RAC. Okubo *et al.* also reported changes in gastric mucosal patterns observable by magnifying NBI.[16] The patterns of enlarged or elongated pits improved to small oval or pinhole-like round pits, and the density of fine irregular vessels decreased. However, a 5-year follow-up study using conventional endoscopy by Oda *et al.* reported that although histological atrophy improved, endoscopic examination revealed no consistent alteration in atrophic border.[26] Antral erosion became more conspicuous 5 years after successful eradication. Spotty redness in the corpus disappeared after 5 years.

The present study has limitations. Assessment of endoscopic findings depended on the endoscopist; however, a meeting was held to agree upon standards for endoscopic assessment. Because endoscopic change varies with the interval after successful eradication, short-term change is never relevant.

In conclusion, assessment of spotty redness after eradication treatment is useful in the diagnosis of *H. pylori* eradication.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflict of interests for this article.

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Original Article

Diagnosis of *Helicobacter pylori* infection in gastric mucosa by endoscopic features: A multicenter prospective study

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Background: Endoscopic features corresponding to pathological findings in the Sydney System have not been identified, and endoscopic diagnosis of chronic gastritis has not yet been established. To establish the diagnosis of *Helicobacter pylori* (*H. pylori*) infection in gastric mucosa by endoscopic features, a prospective multicenter study was carried out.

Patients and Methods: Two hundred and ninety-seven registered patients from 24 facilities between March 2008 and February 2009 were enrolled. Association between endoscopic findings (conventional findings and indigocarmine contrast (IC) method findings) and diagnosis of *H. pylori* infection made by microscopic observation of biopsy specimens was investigated in the corpus and antrum and their diagnostic accuracies were investigated.

Results: Two hundred and seventy-five patients were analyzed. The area under the receiver operating characteristic (ROC) curve for *H. pylori* infection of conventional endoscopy was 0.811 in the corpus and 0.707 in the antrum ($P = 0.006$). Evaluation of diffuse redness, spotty redness and mucosal swelling by conventional endoscopy and swelling of areae gastricae by the indigocarmine contrast (IC) method were useful for diagnosing *H. pylori* infection. Regular arrangement of collecting venules (RAC) in the angle, fundic gland polyposis, hemorrhagic erosion and bleeding spot in the corpus and red streaks, and erosions (flat, raised, hemorrhagic and bleeding spot) in the antrum may be used as diagnostic features suggesting negative *H. pylori* infection.

Conclusion: It is suggested that endoscopic diagnosis of *H. pylori* infection in gastric mucosa by conventional endoscopy and the IC method is mostly possible.

Key words: conventional endoscopy, endoscopic diagnosis, *H. pylori* infection, indigocarmine contrast method, multicenter prospective study

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INTRODUCTION

VARIOUS ENDOSCOPIC CLASSIFICATIONS of chronic gastritis have been proposed, but no integrated classification has been accepted worldwide. Upon the discovery of *Helicobacter pylori* (*H. pylori*), the Sydney System was proposed as a new concept of chronic gastritis in 1991.[1,2] This system comprises pathology and endoscopy sections, and the pathology section has been widely accepted and used worldwide. In contrast, endoscopic features corresponding to pathological findings have not been identified in the endoscopy section, and the diagnosis of *H. pylori* infection in gastric mucosa by endoscopic features has not yet been established.[3–12]

To establish the endoscopic diagnosis of chronic gastritis, the Japan Gastroenterological Endoscopy Society founded

the Study Group for Establishing Endoscopic Diagnosis of Chronic Gastritis. Of the histological findings described in the pathology section of the Sydney System, the relationship between *H. pylori* infection and endoscopic findings, particularly conventional endoscopic findings and chromoendoscopic findings by spraying indigocarmine solution (indigocarmine contrast [IC] method[13,14]) in the stomach currently infected with *H. pylori*, and their diagnostic accuracies were investigated in a multicenter study.

METHODS

Study population

THIS WAS A prospective multicenter study in which 24 facilities participated. In these facilities, at least several specialized endoscopists with experience of 15 years or longer were present.

Patients who met the inclusion criteria described below and gave consent were consecutively registered at each facility between March 2008 and February 2009. The inclusion criteria were patients 40 years or older judged as requiring endoscopy by physicians in charge during a normal consultation. The disease indicated for the registration was chronic gastritis or cases with a non-*H. pylori*-infected stomach.

Patients with the following conditions were excluded: severe liver, renal, and cardiopulmonary dysfunctions, treatment with non-steroidal anti-inflammatory drugs (NSAIDs), antiplatelet agents, anticoagulants, steroids, antibiotics, and proton pump inhibitors (PPI) within 4 weeks before study initiation, previous diagnoses of early and advanced gastric cancer, gastrectomy, diagnosis of *H. pylori* infection, previous treatment with bacterial eradication, previous gastric or duodenal ulcer or scar, blood diseases including anemia, and hemorrhagic tendency.

This study was approved by the ethics committee of each participating facility and carried out in conformity with the Declaration of Helsinki. Written consent was obtained from the subjects.

Procedures

Association between endoscopic findings and diagnosis of *H. pylori* infection made by microscopic observation of biopsy specimens was investigated in the corpus and antrum. Serum anti-*H. pylori* antibody level was measured with E-Plate 'Eiken'[15] (Eiken Chemical Co., Tokyo, Japan) using the *H. pylori* antibody method, and compared with the microscopic diagnosis of *H. pylori* infection. The primary endpoint was the diagnostic characteristics of overall endoscopic findings of *H. pylori* infection individually in the corpus and antrum. Additionally, the secondary endpoint was the diagnostic characteristics of each endoscopic finding of *H. pylori* infection individually in the corpus and antrum.

Endoscopic examination

To judge mucosal color, such as redness, based on consistent criteria, only scopes from Olympus Co. (Tokyo, Japan) were used. High-resolution electronic endoscopes through which collecting venules could be clearly observed (GIF240 and GIF260 series) were used. The IC method was carried out after completion of conventional observation only at facilities that use it in routine clinical practice. In the IC method, the target region was directly sprayed with 0.2% indigocarmine solution.

The characteristics of 15 endoscopic features were defined mainly based on endoscopic division of the Sydney System. Their definitions and characteristics are shown in Table 1. The presence or absence of each endoscopic feature was evaluated on endoscopy following the judgment criteria. Typical endoscopic views are shown in Figure 1. Of the endoscopic findings, when one of diffuse redness, spotty redness, enlarged/tortuous folds, and nodular change was observed, the case was judged as endoscopic *H. pylori* positive.

To standardize endoscopic findings and make uniform the diagnostic accuracy among the participating facilities and observing physicians, the endoscopic findings were sufficiently explained before study initiation, and abstracts of endoscopic findings summarizing typical endoscopic views to be evaluated were distributed to educate physicians. In addition, prior to the start of the study, a pilot study was conducted in 10 patients per institute.

Histological examination

Biopsy specimens were collected at five sites according to the Sydney System recommendation: the greater and lesser (a site 2–3 cm oral from the pyloric ring) curvatures of the antrum; lesser curvature of the angulus; and greater and lesser curvatures of the middle corpus. The biopsy specimens were stained with hematoxylin-eosin (HE staining), and the presence or absence of *H. pylori* infection was microscopically investigated.[16] When the microscopic diagnosis of *H. pylori* infection was doubtful, the preparation was subjected to immunostaining to make a definite diagnosis. When *H. pylori* was positive at one of the five biopsy sites, the stomach was judged as *H. pylori* infection positive. When one or both of the two corpus sites were *H. pylori* positive, the corpus was judged as *H. pylori* infection positive, and when one or both of the two antral sites were *H. pylori* positive, the antrum was judged as *H. pylori* infection positive. When one or more sites were biopsied and all biopsied sites were *H. pylori* negative, the stomach was

Table 1 Definitions and characteristics of each endoscopic feature of the Sydney System

Diffuse redness
Diffuse redness refers to uniform redness involving the entire mucosa of the fundic gland.
Absent: Light orange/yellow to white mucosa
Present: Marked–slight redness is observed.
Spotty redness
Spotty redness refers to multiple, spotty, minor redness of the fundic gland mucosa.
Enlarged/tortuous folds
Enlarged/tortuous folds whose surfaces are neither smooth, nor with a regular width, shows fold thickness and tortuosity.
Mucosal swelling (conventional endoscopy)
(1) It is soft, thick, and distended in fundic gland mucosa. Swollen gastric area-like, convexo-concave mucosa is sometimes observed.
(2) It is soft and convexo-concave in pyloric gland mucosa.
Swelling of areae gastricae (conventional endoscopy)
It is characterized as gastric area-like structure or minor, swollen, soft, hill-like mucosa in fundic gland mucosa.
Swelling of areae gastricae (indigocarmine method)
In the swollen gastric area, the inter-area groove is narrow, and the width is irregular. The gastric area surface is swollen but has no wrinkle. In the gastric area without swelling, there is no apparent distension, and the contour of the gastric area is irregular.
Nodular change
Nodular protrusions measuring 2–3 mm are uniformly distributed in the gastric angle to antrum.
Patchy redness
Localized red areas of various sizes are often observed on white mucosa after *H. pylori* eradication. Redness after erosion healing is also noted as patchy redness.
Red streak
Longitudinal redness identical to 'Kammroetung' in German, which appears as red streaking.
Regular arrangement of collecting venules (RAC)
Minute starfish-like spots in a regular arrangement are visible in fundic gland mucosa without *H. pylori* infection.
Fundic gland polyposis
Various sizes of sessile polyps are seen in fundic gland mucosa.
Erosion
(1) Flat type
Various sizes of flat mucosal defects with whitish-greyish patches.
(2) Raised type
Discrete elevated mucosa with white excavation at the center.
(3) Hemorrhagic erosion
Erosion with bleeding
(4) Bleeding spot
Punctate red spots or dark blackish ecchymotic spots, streaks or flecks.

judged as *H. pylori* infection negative. Similarly, when one or more sites were biopsied in the corpus and antrum, respectively, and all sites were *H. pylori* negative, the regions were judged as *H. pylori* infection negative, respectively.

All pathological judgments were made by a single pathologist with more than 40 years of experience. The pathologist was not informed of the endoscopic diagnosis results.

Statistical analysis

Consistency between the pathological diagnosis and serum antibody measurement was investigated using the κ-value. Regarding the association between the endoscopic findings and *H. pylori* infection, the area under the curve of receiver operating characteristics (ROC/AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and 95% confidence intervals of these were calculated with regard to judgments at the sites and diagnostic characteristics of individual findings. Evaluation was separately made in the entire stomach, the corpus and antrum, and the association between *H. pylori* infection of the stomach and individual findings was investigated. Findings considered difficult to endoscopically judge by endoscopists were excluded from the evaluation. For comparison of testing characteristics between the corpus and antrum, the χ^2-test was used. For comparison of ROC, the test for the

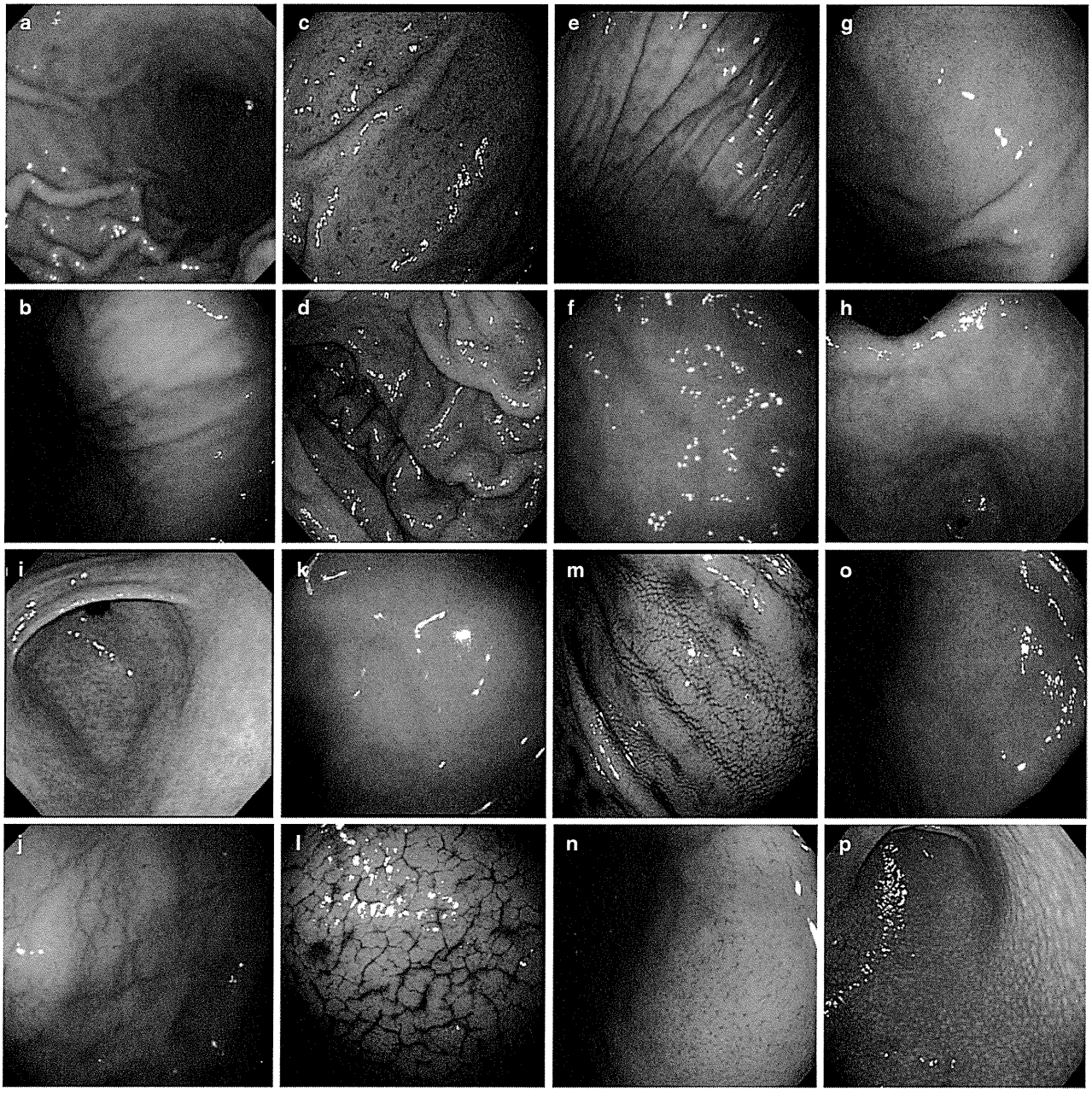

Figure 1 Evaluated endoscopic features. (a) Diffuse redness; present. (b) Diffuse redness: absent. (c) Spotty redness. (d) Fold enlargement: present. (e) Fold enlargement: absent. (f) Mucosal swelling in fundic mucosa: present. (g) Mucosa swelling in fundic mucosa: absent. (h) Mucosal swelling in pyloric mucosa: present. (i) Mucosal swelling in pyloric mucosa: absent. (j) Swelling of areae gastricae (conventional endoscopy): present. (k) Swelling of areae gastricae (conventional endoscopy): absent. (l) Swelling of areae gastricae (indigocarmine [IC] method): present. (m) Swelling of areae gastricae (IC method): absent. (n) Regular arrangement of collecting venules: present. (o) Regular arrangement of collecting venules: absent. (p) Nodular change. (q) Patchy redness. (r) Red streak. (s) Fundic gland polyposis. (t) Flat erosion. (u) Raised erosion. (v) Hemorrhagic erosion. (w) Bleeding spot.

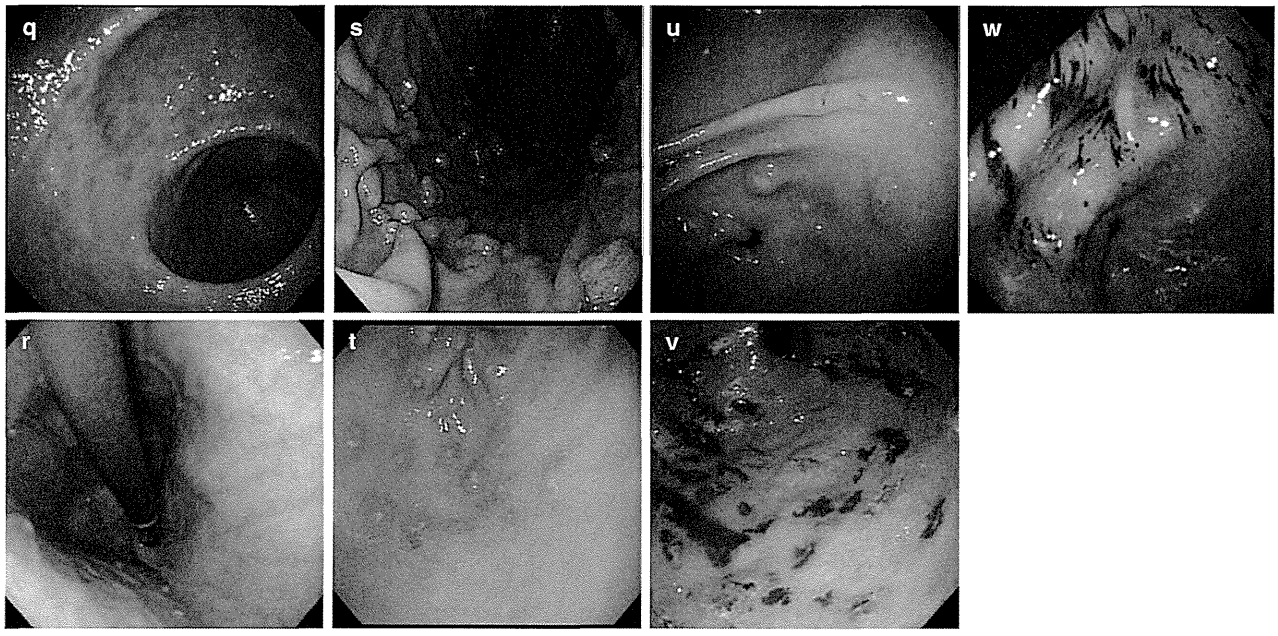

Figure 1 Continued.

equality of the area under the curve was used. ROC/AUC on a combination of two findings was determined based on logistic regression. $P < 0.05$ was regarded as significant.

The target number of registered cases was set at 300 in consideration of dropouts, aiming at a 95% confidence interval of within ± 8% when 130 cases were *H. pylori* positive and the sensitivity of endoscopic findings was 0.8. STATA ver. 11 (StataCorp, College Station, TX, USA) was used for analysis.

RESULTS

OF 297 REGISTERED patients, 275 were analyzed, excluding 22 who were not considered eligible, as no histological examination was carried out in 12, nine were younger than 40 years of age, and *H. pylori* eradication was carried out.

Regarding the baseline characteristics of the patients, there were 127 male and 148 female patients, and the mean age (SD) was 64.6 (9.3) and 64.7 (11.6) years, respectively. *H. pylori* infection was positive in 147 (53.4%) and negative in 128 (46.5%) cases, the age was 64.7 ± 9.3 years in the former and 64.6 ± 11.6 years in the latter, and the positive rate was 57.4% (73/127) in males and 50% (74/148) in females, showing no significant difference.

Consistency between the histological and serum antibody (anti-*H. pylori* immunoglobulin [Ig]G) evaluation was 92.9% and the κ-value was 0.856, showing favorable consistency.

The most frequent finding reported as difficult to judge by endoscopists was swelling of areae gastricae in the corpus mucosa, observed in 38 cases on conventional endoscopy. Other endoscopic findings difficult to judge were observed in a maximum of 13 cases.

Associations between the overall endoscopic and histological evaluation for *H. pylori* infection in the corpus and antrum are shown in Table 2. Regarding the overall diagnostic performance for *H. pylori* infection with conventional endoscopy, the ROC/AUC was 0.811 (95% CI: 0.764–0.858) in the corpus and 0.707 (95% CI: 0.651–0.764) in the antrum, showing that the diagnostic performance was high in the corpus and significantly higher in the antrum ($P = 0.006$). The sensitivity was also high in both the corpus (94.3%, 95% CI: 89.1–97.5) and the antrum (88.1%, 95% CI: 80.5–93.5), and significantly higher in the corpus than in the antrum ($P = 0.001$). The specificity was low in both the corpus and the antrum, and no significant difference was noted between the two regions ($P = 0.342$).

Associations between the endoscopic findings in the corpus and *H. pylori* infection are shown in Table 3. Regarding *H. pylori* infection-positive findings on conventional endoscopy, the ROC/AUC of diffuse redness was high (0.793, 95% CI: 0.742–0.844), followed by 0.737 (95% CI: 0.685–0.790) for mucosal swelling, 0.725 (95% CI: 0.669–0.780) for spotty redness, and 0.725 (95% CI: 0.669–0.781) for swelling of areae gastricae, but that of changes in folds was low (0.690, 95% CI: 0.636–0.744). When cases positive

Table 2 Diagnostic value of conventional endoscopic findings for *H. pylori* infection

	H. pylori positive	*H. pylori* negative	Total	ROC/AUC	Sensitivity % (95% CI)	Specificity % (95% CI)
Corpus						
Endoscopically *H. pylori* positive	133	48	181	0.811 (0.764–0.858)	94.3 (89.1–97.5)	62.8 (53.8–71.1)
Endoscopically *H. pylori* negative	8	81	89			
Antrum						
Endoscopically *H. pylori* positive	96	75	171	0.707 (0.651–0.764)	88.1 (80.5–93.5)	52.8 (44.8–60.8)
Endoscopically *H. pylori* negative	13	84	87			
P-value				0.006	0.001	0.342

ROC/AUC, area under the curve of receiver operating characteristics.

Table 3 Diagnostic value of endoscopic features in the corpus for *H. pylori* infection

		H. pylori positive	*H. pylori* negative	Total	ROC/AUC (95% CI)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
Diffuse redness	+	121	43	164	0.793	83.4	66.9	73.8	78.4
	–	24	87	111	(0.742–0.844)	(76.4–89.1)	(58.1–74.9)	(66.4–80.3)	(69.6–85.6)
Spotty redness	+	102	34	136	0.725	70.3	73.8	75.0	69.1
	–	43	96	139	(0.669–0.780)	(62.2–77.6)	(65.4–81.2)	(66.9–82.0)	(60.7–76.6)
Enlarged/tortuous fold	+	83	25	108	0.690	58.5	79.5	76.9	62.2
	–	59	97	156	(0.636–0.744)	(49.9–66.7)	(71.3–86.3)	(67.8–84.4)	(54.1–69.8)
Mucosal swelling	+	94	24	118	0.737	67.1	80.3	79.7	68.1
	–	46	98	144	(0.685–0.790)	(58.7–74.8)	(72.2–87.0)	(71.3–86.5)	(59.8–75.6)
Swelling of areae gastricae									
Conventional	+	78	21	99	0.725	63.4	81.6	78.8	67.4
	–	45	93	138	(0.669–0.781)	(54.3–71.9)	(73.2–88.2)	(69.4–86.4)	(58.9–75.1)
IC method	+	72	16	88	0.804	77.4	83.3	81.6	79.2
	–	21	80	101	(0.747–0.861)	(67.6–85.4)	(74.4–90.2)	(72.2–89.2)	(70.0–86.6)
Nodular change	+	2	0	2	0.507	1.4	100	100	48.0
	–	141	130	271	(0.497–0.517)	(0.2–5.0)	(97.2–100)	(15.8–100)	(41.9–54.1)
Patchy redness	+	44	17	61	0.589	30.8	86.9	72.1	53.3
	–	99	113	212	(0.541–0.636)	(23.3–39.0)	(79.9–92.2)	(59.2–82.9)	(46.3–60.2)
Red streak	+	8	28	36	0.580	5.5	78.5	22.2	42.7
	–	137	102	239	(0.540–0.620)	(2.4–10.6)	(70.4–85.2)	(15.8–100)	(36.3–49.2)
RAC	+	9	60	69	0.708	6.4	52.0	13.0	33.2
	–	131	65	196	(0.659–0.756)	(3.0–11.9)	(42.9–61.0)	(6.1–23.3)	(26.6–40.2)
Fundic gland polyposis	+	3	31	34	0.610	2.1	76.0	8.8	40.8
	–	142	98	240	(0.571–0.649)	(0.4–5.9)	(67.7–83.1)	(1.9–23.7)	(34.6–47.3)
Erosion									
Flat	+	6	14	20	0.533	4.1	89.2	30.0	45.5
	–	139	116	255	(0.502–0.564)	(1.5–8.8)	(82.6–94.0)	(11.9–54.3)	(39.3–51.8)
Raised	+	5	5	10	0.502	3.4	96.2	50.0	47.2
	–	140	125	265	(0.480–0.524)	(1.1–7.9)	(91.3–98.7)	(18.7–81.3)	(41.0–53.4)
Hemorrhagic	+	1	5	6	0.516	0.7	96.2	16.7	46.5
	–	144	125	269	(0.498–0.534)	(0.0–3.8)	(91.3–98.7)	(0.4–64.1)	(40.4–52.6)
Bleeding spot	+	3	15	18	0.547	2.1	88.5	16.7	45.3
	–	139	115	254	(0.517–0.577)	(0.4–6.0)	(81.7–93.4)	(3.6–41.4)	(39.0–51.6)

+, present; –, absent. IC, indigocarmine; NPV, negative predictive value; PPV, positive predictive value; RAC, regular arrangement of collecting venules; ROC/AUC, area under the curve of receiver operating characteristics.