Endoscopic atrophic classification before and after *H. pylori* eradication is closely associated with histological atrophy and intestinal metaplasia

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submitted 3. March 2015
accepted 16. March 2015

Bibliography
DOI http://dx.doi.org/10.1055/s-0034-1392090
Published online: 26.5.2015
Endosc Int Open 2015; 03: E311–E317

E-ISSN 2196-9736

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Background and study aims: The relationship between endoscopic atrophy classification (EAC) and histological gastric atrophy and intestinal metaplasia (IM) was examined before and after *Helicobacter pylori* (*H. pylori*) eradication in order to evaluate the usefulness of EAC for detecting the risk of gastric cancer following eradication.

Patients and methods: A total of 230 patients (137 males, 93 females; mean age: 58.0 ± 11.8 y) with successful eradication were enrolled. EAC score was defined as follows: C0(none): 0, C1: 1, C2: 2, C3: 3, O1: 4, O2: 5, and O3(severe): 6. Histological atrophy and IM score (0 to 3) from the antrum and the corpus were evaluated with updated Sydney system for histological atrophy and IM.

Results: The mean EAC scores were 3.46 before eradication and 3.20 after eradication ($P=0.026$). The mean atrophy scores before and after eradication were 1.45 and 0.92 at the antrum ($P<0.001$) and 0.50 and 0.07 at the corpus ($P<0.001$), respectively. The mean IM scores before and after eradication were 0.55 and 0.47 at the antrum ($P=0.154$), and 0.09 and 0.05 at the corpus ($P=0.096$), respectively. The histological atrophy scores showed significant improvement after eradication, while IM showed no significant change. The Mantel-Haenszel test for trend indicated there was a significant correlation between EAC and histological atrophy and IM, except antral atrophy after eradication.

Conclusions: EAC exhibited a significant correlation between histological atrophy and IM, and represents a noninvasive classification method. EAC may be beneficial in evaluating the risk of gastric cancer after *H. pylori* eradication.

Introduction

Helicobacter pylori (*H. pylori*) infection has been recognized as a major pathogen of gastric cancer [1,2]. Correspondingly, several reports have indicated that *H. pylori* eradication therapy mediates a preventive effect against gastric cancer development [3–6]. However, gastric cancer was still found to persist in some cases. Therefore, a more simple and straightforward observation method is necessary to monitor gastric cancer following *H. pylori* eradication.

Histological gastric atrophy and intestinal metaplasia (IM) are regarded as precancerous lesions, and are recognized as risk factors both before and after *H. pylori* eradication [2,7]. Endoscopic atrophy classification (EAC) according to Kimura and Takemoto [8] has frequently been used to evaluate the atrophic degree of gastric mucosa. Moreover, the degree of EAC has been found to correlate with the degree of histological atrophy [8,9]. However, these studies do not mention the correlation between EAC and atrophy and IM after eradication. In addition, EAC is associated with the incidence of gastric cancer after eradication [10], and provides a noninvasive method for predicting gastric cancer after eradication compared with biopsy of gastric mucosa [10,11].

While *H. pylori* eradication has been shown to reduce the degree of gastric atrophy and IM [12–15], the correlation between EAC and post-*H. pylori* eradicated gastric mucosa and, in particular, atrophy and IM status has not been investigated yet. Therefore, in this study, the relationship between EAC and histological gastric atrophy and IM not only before but also after *H. pylori* eradication was examined in order to evaluate the usefulness of EAC for detecting the risk of gastric cancer following *H. pylori* eradication.

Patients and Methods

A total of 325 patients who underwent upper gastrointestinal endoscopy and had examination for detection of *H. pylori* at Oita University Hospital

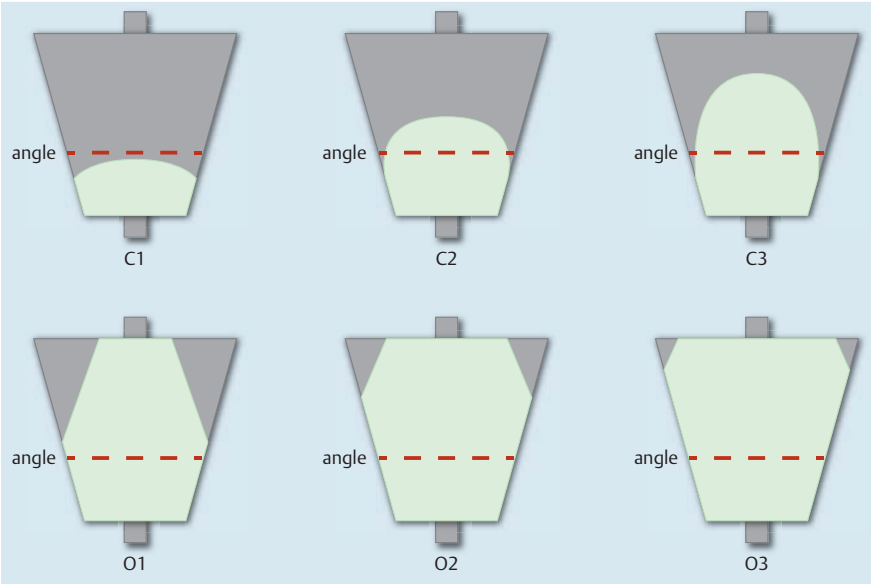

Fig. 1 Extension of atrophic border of Kimura-Takemoto classification [8]. The atrophy range was shown with light gray.

between January 1995 and December 2010 were enrolled in this study. The patients with *H. pylori* infection subsequently underwent *H. pylori* eradication. These subjects were examined repeatedly with endoscopy more than 3 years after *H. pylori* eradication in order to survey gastric mucosal alteration after eradication. All study protocols were approved by an institutional review board. To detect *H. pylori*, patients underwent at least one of the following assays: a rapid urease test (RUT), histology, culture testing, and/or a urea breath test (UBT). A subset of patients underwent all of the assays. Only histology and culture tests were used for *H. pylori* diagnosis until RUT and UBT were developed.

After confirming the safety of eradication therapy and obtaining further informed consent, patients with *H. pylori* were administered a proton pump inhibitor-based combination therapy. Briefly, between 4 weeks and 6 months after completing eradication therapy, RUT, histology, cultures, and/or UBT examinations were repeated. *H. pylori* eradication was considered successful if all tests were negative. *H. pylori*-negative cases and cases involving *H. pylori* recrudescence or reinfection were excluded. Endoscopies were also repeated for patients who underwent successful *H. pylori* eradication. The endoscopic findings performed 78.05 ± 36.72 (range 36 – 153) months after eradication were evaluated for this study.

Endoscopic evaluation

The endoscopic examinations were performed using an Olympus electroscope (model Q-240, 260, HQ-260, and others; Tokyo, Japan). Endoscopic atrophy was defined using an endoscopic-atrophic-border scale previously reported by Kimura and Takemoto [8]. This scale correlates with histological results [8, 9] and includes the following classifications: 1) close-type, when the atrophic border remains on the lesser curvature of the stomach; and 2) open-type, when the atrophic border extends along the anterior and posterior walls of the stomach and is not associated with the lesser curvature of the stomach. Close-type and open-type atrophy were further classified as none (C0), mild (C1, 2), moderate (C3, O1), and severe (O2, 3) atrophy (**Fig. 1**). In this study, atrophy grade were also scored as C0: 0, C1: 1, C2: 2, C3: 3, O1: 4, O2: 5, and O3: 6 respectively, with 0 representing an absence of atrophy and 6 indicating severe atrophy.

Histological evaluation

Biopsies were performed prior to eradication in order to diagnose *H. pylori*. Biopsy specimens were obtained from the greater curvature of the antrum and the greater curvature of the corpus, which are two of five points recommended by updated Sydney system [16]. Gastric mucosa samples were subsequently evaluated according to updated Sydney system with the degree of inflammation, neutrophil activity, atrophy, and IM classified as: 0, 'normal'; 1, 'mild'; 2, 'moderate'; and 3, 'marked'. Grade of histological gastritis was evaluated with this score 0, 1, 2, and 3. Histological evaluations were performed by two experienced pathologists from Oita University Hospital. Correlations between endoscopic atrophy classification scores and histological atrophic scores were evaluated before and after *H. pylori* eradication.

Statistical analysis

Statistical analyses were performed using SPSS software (PASW Statistics 18, SPSS Japan), and data are expressed as the mean ± standard deviation. Student's *t*-test was performed to compare updated Sydney system scores before and after eradication. The Mantel-Haenszel test for trend was used to compare endoscopic atrophic degree, histological gastric atrophy, and IM. *P*-values less than 0.05 were considered significant.

Results

Disease history

Of 325 subjects, those who were *H. pylori*-negative or had unsuccessful eradication or recurrence of *H. pylori* infection were excluded (**Fig. 2**). Forty-three cases were lost during observation. A total of 230 patients (137 males, 93 females) were analyzed. The mean age of this cohort at the time of eradication was 58.0 ± 11.8 y. The cohort was also characterized by a history of chronic gastritis (n = 105), gastric ulcers (n = 54), duodenal ulcers (n = 45), gastroduodenal ulcers (n = 13), gastric cancer (n = 7), gastric adenoma (n = 1), and mucosal-associated lymphoid tissue lymphoma (n = 5).

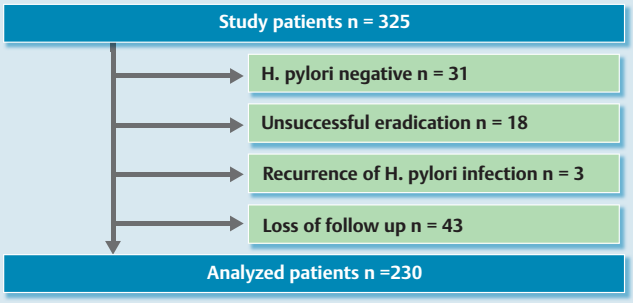

Fig. 2 Follow-up flowchart of patients

Endoscopic gastric atrophy

Prior to *H. pylori* eradication, the endoscopic atrophic grades assigned to the cohort included: C1 (n=22), C2 (n=47), C3 (n=41), O1 (n=61), O2 (n=36), and O3 (n=23). After eradication, endoscopic findings that were performed 78.05±36.72 (range 36–153) months after eradication were evaluated. The results of endoscopic examination at the beginning and the end of the observation period were assessed. The endoscopic grades were C1 (n=20), C2 (n=58), C3 (n=59), O1 (n=50), O2 (n=31), and O3 (n=12). Compared with the grades assigned before eradication, an improvement in endoscopic grade was observed following successful eradication in 94 cases, while no change or exacerbation of atrophy was observed in 78 cases and 58 cases, respectively. The mean endoscopic gastric atrophy score for all of the cases was 3.46±1.43 before eradication and significantly reduced to 3.20±1.33 after eradication (P=0.026).

Histological atrophy and IM

The mean atrophy scores before and after eradication for all of the cases were: 1.45±0.05 and 0.92±0.05 at the antrum (P< 0.001) and 0.50±0.05 and 0.07±0.02 at the corpus (P<0.001), respectively in each case. The mean IM scores before and after eradication were 0.55±0.06 and 0.47±0.05 at the antrum (P= 0.154) and 0.09±0.02 and 0.05±0.02 at the corpus (P=0.096), respectively in each case. Atrophy scores at both the antrum and the corpus showed significant improvement following eradication. However, IM scores showed no significant change at either site.

Comparison of endoscopic and histological findings

Fig. 3 presents the endoscopic and histological atrophy and IM before and after eradication. Seven years after successful eradication, EAC improved from O2 (**Fig. 3a, b**) to C3 (**Fig. 3c, d**). Histological atrophy also improved 2 to 0 after eradication at both the antrum (**Fig. 3f, h**) and the corpus (**Fig. 3e, g**). Similarly, the IM score at the antrum improved from 2 to 0 (**Fig. 3f, h**). **Fig. 4** presents another case. Seven years after successful eradication, this case did not show improvement in EAC, with scores of O2 (**Fig. 4a, b**) to O2 (**Fig. 4c, d**). However, histological atrophy improved from 2 to 0 after eradication at both the antrum (**Fig. 4f, h**) and corpus (**Fig. 4e, g**). The IM score at the antrum also improved from 1 to 0 (**Fig. 4f, h**).

Comparison of endoscopic and histological atrophy and IM scores

At the antrum, the histological atrophy scores before and after eradication for each endoscopic grade were: C1: 1.05 and 0.74 (P=0.104); C2: 1.32 and 0.90 (P=0.004); C3: 1.40 and 0.91 (P= 0.003); O1: 1.56 and 1.05 (P<0.001); O2: 1.53 and 0.92 (P= 0.003); O3: 1.63 and 1.20 (P=0.059), respectively (**Fig. 5a**).

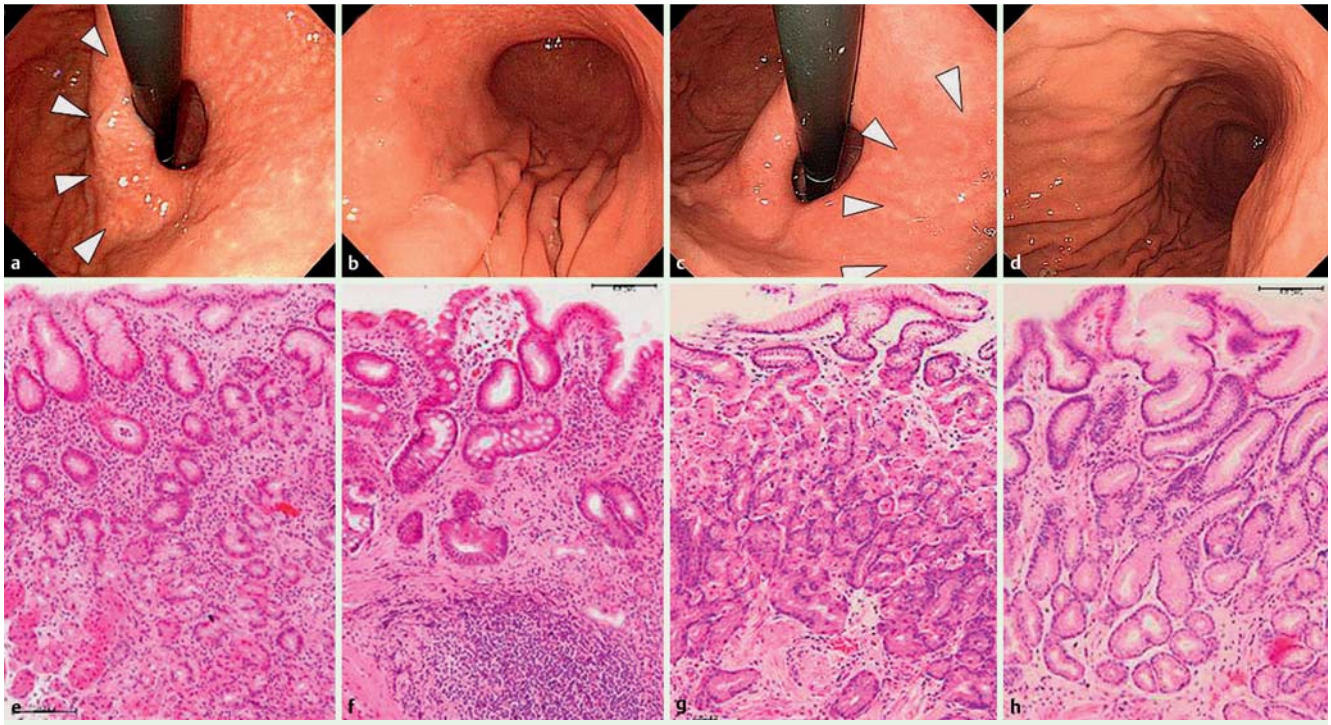

Fig. 3 Relationship between endoscopic and histological findings. Endoscopic findings before (**a, b**) and 7 years after eradication (**c, d**) (white arrows: atrophic border) showed atrophy improvement. Histological findings at the corpus (**e**) and antrum (**f**) before eradication showed improvement at the corpus (**g**) and antrum (**h**) after eradication.

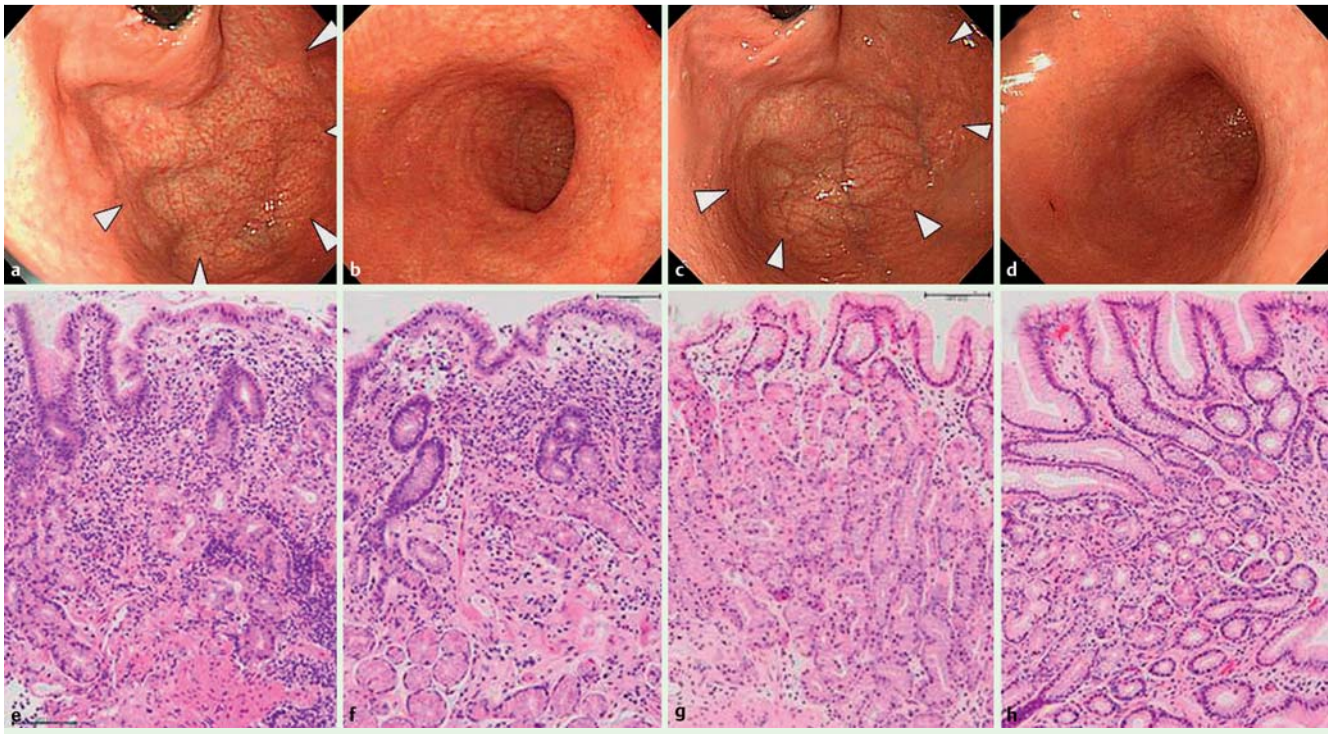

Fig. 4 Relationship between endoscopic and histological findings. Another case of endoscopic findings before eradication (**a, b**) and 7 years after eradication (**c, d**) (white arrows: atrophic border) showed no improvement. Histological findings at the corpus (**e**) and antrum (**f**) before eradication improved at the corpus (**g**) and antrum (**h**) after eradication.

Atrophy scores, except C1 and O3, showed significant reductions following eradication. At the corpus, the histological atrophy scores before and after eradication for each endoscopic grade were: C1: 0.26 and 0.00 (P=0.028); C2: 0.28 and 0.02 (P=0.003); C3: 0.51 and 0.04 (P<0.001); O1: 0.56 and 0.11 (P<0.001); O2: 0.70 and 0.04 (P<0.001); O3: 0.74 and 0.50 (P=0.29), respectively (**Fig. 5b**). Atrophy scores, except for O3, showed significant reductions following eradication.

The P-value for the Mantel-Haenszel test for trend was 0.008 before eradication and 0.069 after eradication at the antrum, and was 0.004 before eradication and 0.031 after eradication at the corpus. The trend in EAC and histological atrophy was significant before eradication and after eradication, except at the antrum after eradication (**Fig. 5a, b**). At the antrum, the histological IM scores before and after eradication for each endoscopic grade were: C1: 0.21and 0.21 (P=0.50); C2: 0.31and 0.26 (P=0.35); C3: 0.72 and 0.47 (P=0.11); O1: 0.56 and 0.59 (P=0.43); O2: 0.73 and 0.69 (P=0.45); O3: 0.90 and 1.10 (P=0.32), respectively (**Fig. 6a**). At the corpus, the histological IM scores before and after eradication for each endoscopic grade were: C1: 0.00 and 0.05 (P=0.17); C2: 0.02 and 0.00 (P=0.16); C3: 0.08 and 0.00 (P=0.092); O1: 0.09 and 0.06 (P=0.38); O2: 0.18 and 0.08 (P=0.18), O3: 0.26 and 0.50 (P=0.27), respectively (**Fig. 6b**). None of the IM scores after eradication for any of EAC levels exhibited any significant improvement at both the antrum and the corpus. The P-value for the Mantel-Haenszel test for trend was 0.005 before eradication and <0.0001 after eradication at the antrum, and 0.048 before eradication and 0.027 after eradication at the corpus. EAC and histological IM showed a significant trend both before and after eradication (**Fig. 6a, b**).

Discussion

Although *H. pylori* eradication has the potential to prevent gastric cancer, recurrence of gastric cancer has been observed following *H. pylori* eradication [4–6, 17, 18]. Therefore, the incidence of gastric cancer recurrence after *H. pylori* eradication remains to be fully characterized. Although molecular factors predictive of gastric cancer are useful [19, 20], simpler methods are believed to be desirable. Atrophy and IM have been recognized as risk factors for gastric cancer following *H. pylori* eradication [10, 11, 21–23]. Intestinal-type gastric cancer, appears to undergo a multistep carcinogenic process, from atrophic gastritis to IM to dysplasia [7]. To identify high-risk factors for cases of gastric cancer that develop after *H. pylori* eradication, a minimally invasive method, such as endoscopic findings without biopsy, is needed. In general, annual endoscopy has been reported to be useful in detecting most new tumors, and is associated with improved rates of survival [24]. Therefore, endoscopic surveillance after eradication is considered to be very important. Current results cannot identify the surveillance period that is optimal in each individual case. Further examination is necessary to identify the optimal surveillance period for low-risk and high-risk patients. The use of specific wavelengths of light, such as magnifying narrow-band imaging [25–27] for performing endoscopies has been used recently. Currently, this method is very useful for gastric cancer surveillance. However, we hypothesize that a more basic and cost-effective observation method may help evaluate gastric cancer development following *H. pylori* eradication. In the current study, a significant correlation between EAC and histological atrophy before eradication was identified, and this result is consistent with that of previous reports [8, 9, 28]. However, to our knowledge, this is the first study to identify a correlation between EAC and histological atrophy both before and after *H. pylori* eradication. Patients with

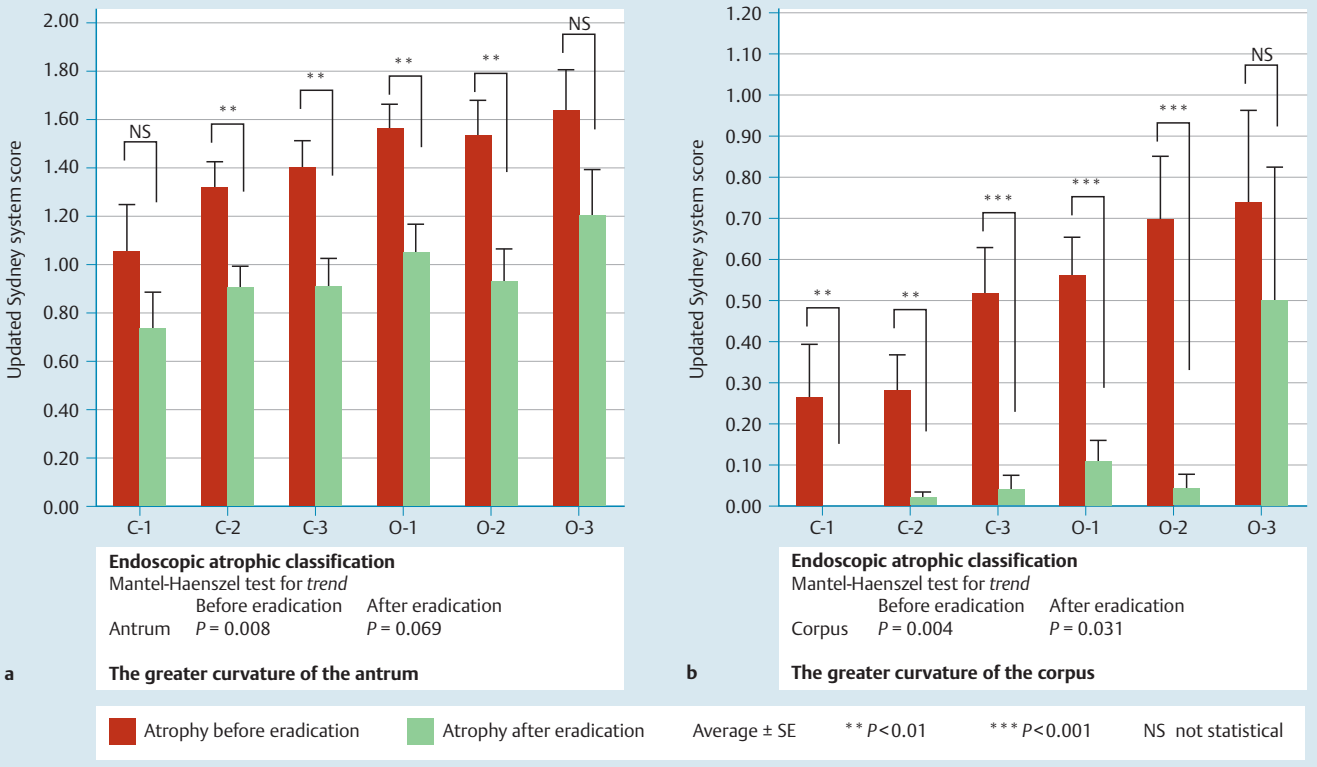

Fig. 5 Relationship between endoscopic atrophy scores and histological atrophy scores before and after *H. pylori* eradication. Each degree of endoscopic atrophy showed significant improvement of histological atrophy following eradication, except for C1 and O3 at the antrum, and O3 at the corpus. Endoscopic atrophy classification showed significant correlation with histological atrophy except antral site after eradication.

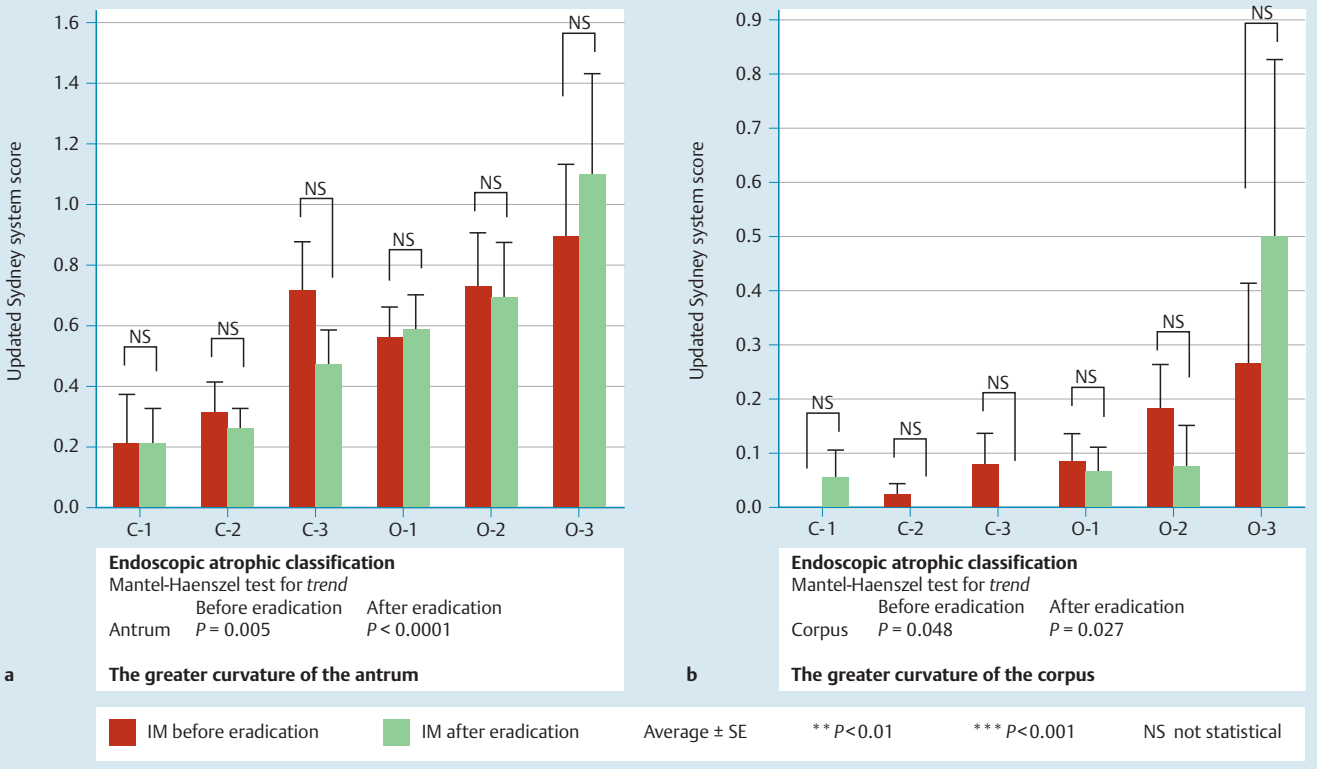

Fig. 6 Relationship between endoscopic atrophy scores and histological IM scores before and after *H. pylori* eradication.Each degree of endoscopic atrophy showed no significant improvement of IM after eradication. Endoscopic atrophy classification showed significant correlation with histological IM at both sites before and after eradication.

severe endoscopic atrophy have a high risk of gastric cancer after eradication [10, 22, 23], and our previous study indicated that patients who develop gastric cancer after eradication exhibit severe endoscopic atrophy and histological antral atrophy compared with patients without gastric cancer [11]. Furthermore, a more severe grade of IM has been observed in gastric cancer cases following eradication [23]. Therefore, it has been hypothesized that EAC is valid to judge gastric cancer risk before *H. pylori* eradication. Although the endoscopic index of successful eradication was evaluated [29], EAC and histological IM have not been compared over a long period of time following eradication. In the current study, EAC and histological atrophy were significantly correlated at the corpus. In addition, almost every degree of endoscopic atrophy that was observed in the current cohort following eradication was accompanied by a significantly low level of histological atrophy compared with levels prior to eradication. These results suggest that there is less improvement in endoscopic atrophy than in histological atrophy following eradication. In **Fig. 4**, histological atrophy and IM are shown to be improved after eradication, while an improvement in endoscopic atrophy was not observed. Thus, the degree of histological atrophy after eradication was milder than that observed before eradication for a similar endoscopic atrophy range.

There was also no significant relation between EAC and histological atrophy at the antrum following eradication. This result is attributed to the observation that severe histological atrophy was remarkably improved following eradication. However, histological IM exhibited a significant correlation with endoscopic atrophy degree at the antrum both before and after eradication. Therefore, as the degree of endoscopic atrophy becomes more extensive, histological IM at the antrum also becomes more extensive, even after *H. pylori* eradication. Moderate-to-severe endoscopic atrophy has been reported to exhibit extensive incomplete IM [30], which is consistent with the IM distribution observed in the current study. Unlike histological atrophy, no significant difference in the degree of histological IM was observed before and after eradication. Many studies have indicated that the gastric mucosa undergoes alterations following *H. pylori* eradication [12–15]. However, in two recent meta-analyses, improvement in atrophic gastritis, but not in IM, was observed following *H. pylori* eradication [13, 14]. In our previous study, histological atrophy was found to improve, however, IM only improved at the lesser curvature of the corpus following eradication [15]. In the current study, no significant alterations in IM before and after eradication were observed, consistent with results of these previous studies. Because the long observation period may have influenced the results of this study, further study of cases involving surveillance during a narrower time period may be necessary.

Regarding the strong correlation between EAC and histological IM, it has been suggested that EAC is a useful index for long-term gastric cancer risk following *H. pylori* eradication. In general, IM does not improve following eradication, neither does dysregulation of micro-RNAs in IM [31]. Taken together, these results suggest that IM should be regarded as one of the most informative factors predictvie of gastric cancer following *H. pylori* eradication. Furthermore, because gastric cancer tends to develop more frequently at the antrum than at the corpus following *H. pylori* eradication [23], the strong association between EAC and histological IM at the antrum may indicate that EAC may not depend on whether screening for gastric cancer is performed before or after *H. pylori* eradication. In conclusion, EAC exhibited a significant correlation with histological atrophy and IM at the antrum and corpus in the gastric mucosa before and after *H. pylori* eradication, except for antral atrophy after eradication. Thus, EAC may be useful for observations of histological atrophy and IM degree independent of invasive biopsies, and it may also be beneficial for evaluating the risk of gastric cancer after *H. pylori* eradication.

Competing interests: None

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