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ABOUT COVER

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Observational Study

Helicobacter pylori-induced inflammation masks the underlying presence of low-grade dysplasia on gastric lesions

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Abstract

BACKGROUND

Helicobacter pylori (*H. pylori*) infection has been associated with a long-term risk of

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precancerous gastric conditions (PGC) even after *H. pylori* eradication.

AIM

To investigate the efficacy of High-Resolution White-Light Endoscopy with Narrow-Band Imaging in detecting PGC, before/after *H. pylori* eradication.

METHODS

We studied 85 consecutive patients with *H. pylori*-related gastritis with/without PGC before and 6 mo after proven *H. pylori* eradication. Kimura-Takemoto modified and endoscopic grading of gastric intestinal metaplasia classifications, were applied to assess the endoscopic extension of atrophy and intestinal metaplasia. The histological result was considered to be the gold standard. The Sydney System, the Operative-Link on Gastritis-Assessment, and the Operative-Link on Gastric-Intestinal Metaplasia were used for defining histological gastritis, atrophy and intestinal metaplasia, whereas dysplasia was graded according to World Health Organization classification. Serum anti-parietal cell antibody and anti-intrinsic factor were measured when autoimmune atrophic gastritis was suspected.

RESULTS

After *H. pylori* eradication histological signs of mononuclear/polymorphonuclear cell infiltration and Mucosal Associated Lymphoid Tissue-hyperplasia, disappeared or decreased in 100% and 96.5% of patients respectively, whereas the Operative-Link on Gastritis-Assessment and Operative-Link on Gastric-Intestinal Metaplasia stages did not change. Low-Grade Dysplasia prevalence was similar on random biopsies before and after *H. pylori* eradication (17.6% *vs* 10.6%, $P = 0.19$), but increased in patients with visible lesions (0% *vs* 22.4%, $P < 0.0001$). At a multivariate analysis, the probability for detecting dysplasia after resolution of *H. pylori*-related active inflammation was higher in patients with regression or reduction of Mucosal Associated Lymphoid Tissue hyperplasia, greater alcohol consumption, and anti-parietal cell antibody and/or anti-intrinsic factor positivity [odds ratio (OR) = 3.88, 95% confidence interval (CI): 1.31-11.49, $P = 0.01$; OR = 3.10, 95% CI: 1.05-9.12, $P = 0.04$ and OR = 5.47, 95% CI: 1.33-22.39, $P < 0.04$, respectively].

CONCLUSION

High-Resolution White-Light Endoscopy with Narrow-Band Imaging allows an accurate diagnosis of Low-Grade Dysplasia on visible lesions after regression of *H. pylori*-induced chronic gastritis. Patients with an overlap between autoimmune/*H. pylori*-induced gastritis may require more extensive gastric mapping.

Key words: Autoimmune gastritis; Dysplasia; Diagnosis; Malignancy; Gastric cancer; Symptoms; Signs

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Core tip: *Helicobacter pylori* (*H. pylori*) infection is commonly responsible for precancerous gastric conditions. Heterogeneous long-term endoscopic follow-up studies (2-16 years), have shown conflicting results on the efficacy of *H. pylori* eradication in reducing the prevalence and histological progression of advanced precancerous gastric conditions. High-Resolution white-light endoscopy combined with narrow-band imaging allows for a more accurate diagnosis of gastric low-grade dysplasia when performed soon after *H. pylori* eradication. Subjects with an overlap between autoimmune and *H. pylori*-induced chronic gastritis should be considered to be at a higher risk for more severe gastric injury and they may require more extensive gastric mapping.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection has been associated with premalignant gastric conditions (PGC), such as chronic atrophic gastritis and intestinal metaplasia (IM), which are strongly associated with dysplasia and Lauren intestinal-type of gastric carcinoma (GC)^[1-7]. Autoimmune atrophic gastritis (AAG) is responsible for progressive mucosal atrophy (antrum-sparing) with or without IM^[8]. Many studies have attributed gastric carcinogenesis to both genetic predisposition and *H. pylori*-induced gastric inflammation^[9-13]. *H. pylori* strains possessing higher cytotoxicity that infect genetically predisposed subjects have been considered responsible for more severe degrees of inflammation and rapid progression to intestinal-type GC^[14-20]. Nowadays, PGC detection and surveillance are considered a cost-effective strategy for the prevention of high-grade dysplasia and GC only in intermediate or high-risk populations^[7]. Heterogeneous long-term endoscopic follow-up studies, with a duration of between 2-16 years, have shown conflicting results on the efficacy of *H. pylori* eradication in reducing the prevalence and histological progression of advanced PGC, and in decreasing GC incidence^[3,21-25]. The current European guidelines recommend *H. pylori* eradication in high-risk subjects^[7,22,26,27]. Nevertheless, even after *H. pylori* eradication, the risk for PGC may remain or even increase in patients undergoing long-term surveillance^[3,22].

A high-quality upper endoscopy should include at least five non-targeted biopsies at the lesser and greater curvatures of the antrum-corpora and at the *incisura angularis* for *H. pylori* infection diagnosis and the optimal detection and staging of advanced PGC, which are randomly distributed across the stomach^[7,28,29]. Additional targeted biopsies of any visible lesions are recommended, since low-grade dysplasia (LGD) and high-grade dysplasia (HGD) may appear as endoscopically evident, depressed, flat, or raised lesions^[7,28,29].

The Sydney System, the Operative-Link on Gastritis-Assessment (OLGA) and the Operative-Link on Gastric-Intestinal Metaplasia (OLGIM) classifications are commonly used to evaluate the histological inflammation and activity due to mononuclear and polymorphonuclear cells infiltration, as well as atrophy and IM, whereas dysplasia is commonly graded according to the World Health Organization classification^[30,31]. During white-light endoscopy (WLE), the Kimura-Takemoto modified classification has been used to assess the extension of atrophy^[32]. Several studies showed that magnification chromoendoscopy (CE) and narrow-band imaging (NBI) with or without magnification performed by expert endoscopists could be more accurate than WLE alone in diagnosing PGC, although random biopsies may detect PGC otherwise undetectable by NBI targeted biopsies. Thus, a combination of both random-WLE and targeted-NBI biopsies is suggested as the most accurate^[29,33-37]. More recent some investigators created and validated a simplified NBI classification, with magnification [(endoscopic grading of gastric intestinal metaplasia (EGGIM)], using reproducible NBI features (based on endoscopic mucosal and vascular patterns)^[29] of the whole gastric mucosa, with an accuracy (resulting from a multicentre study) of 73%, 87% and 92%, for *H. pylori*-infection, IM and dysplasia diagnosis, respectively^[37].

For patients with an indefinite diagnosis for dysplasia, or with dysplasia resulting from random biopsies without endoscopic evidence of visible lesions, the current guidelines suggest an “immediate” endoscopic reassessment with high-resolution endoscopy with NBI to exclude LGD or HGD on missed visible lesions^[7]. This procedure revises what was indicated in previous guidelines^[28], which advised, in such an event, a delayed endoscopic follow-up within one year after the diagnosis^[7,28].

On these premises, supposing that dysplastic lesions might be missed on the background of an active *H. pylori* related gastritis, we focused on the assessment of the combined diagnostic performance of high-resolution white-light endoscopy (HR-WLE) with NBI in detecting PGC, before and 6 mo after *H. pylori* eradication (primary end-point). As a secondary aim we considered some clinical factors, autoimmune laboratory markers, and histopathological features as potential co-factors for the development of dysplastic lesions.

MATERIALS AND METHODS

Study design, patient selection and endoscopic follow-up

This is an observational, prospective study performed at the tertiary care center of the National Institute of Gastroenterology “S De Bellis” (Castellana Grotte, Bari, Italy). Our research was carried out in compliance with the Declaration of Helsinki and with routine clinical practice (Clinical Trial Gov number NCT03917836). All the procedures received local ethics committee approval (Protocol 67/18/CT, 140/18/CE). All patients gave their written informed consent to take part in the study.

From June 2017 to April 2019, we enrolled 85 consecutive subjects, from a cohort study of 156 outpatients, who underwent high-resolution gastroscopies with/without NBI using the Olympus Evis Exera III processor® and Olympus GIF-HQ190® instruments (Olympus Tokyo, Japan). **Figure 1** shows the inclusion and exclusion of enrolment steps.

For patients with suspected AAG, anti-parietal cell antibody (APCA) and anti-intrinsic factor (AIF) were measured in serum using indirect immunofluorescence method and immunoenzimatic assay respectively. APCA antibodies were detected by NOVA Lite® Stomach Kit (Inova Diagnostics, San Diego, CA, United States) and AIF antibodies were detected by an automated assay using a Beckman Coulter Unicel DXI 800 (Beckman Coulter Inc., Fullerton, CA, United States).

The endoscopic procedures were performed by two expert endoscopists (more than 200 HRE-NBI per year), one of whom (AP) was present during all procedures as either operator or supervisor. The statistical review of this study was executed by an experienced biomedical statistician. Based on previously published data^[38], we calculated the sample size for the analysis of the primary outcome using the function `ss2x2` implemented in the package `exact2x2`. We examined that 48 patients (24 controls and 24 treated) would yield a power of 0.82 at a significance level of 0.05. Therefore, we aimed at enrolling at least 48 patients. The study was completed when the 85 enrolled subjects had been endoscopically reassessed with HR-WLE and NBI, and with gastric biopsy samples according to the Sydney System^[28], 6 mo after *H. pylori* eradication confirmed by ¹³C-urea breath-test (¹³C-UBT), in order to identify the diagnostic yield of HR-WLE with NBI in detecting PGC, during this short surveillance time.

¹³C urea breath test was performed under the following conditions: An 8-h fast, mouth washing before dosing, administration of 75 mg ¹³C urea in a water solution, collection of breath samples in two 10-mL glass-sample containers, (at baseline and 20 min) and subjects in a sitting position. The breath samples were analyzed by gas-chromatography-mass spectrometry (GC-MS; ABCA Sercon Gateway, United Kingdom). *H. pylori* infection was considered present if the difference in ¹³C/¹²C between baseline value and 20-min value exceeded 40/00.

Inclusion criteria were as follows: Patients ≥ 18 years undergoing upper gastrointestinal endoscopy for *H. pylori*-related chronic symptoms (*i.e.*, recurrent abdominal pain, dyspepsia, or unexplained anemia), with positivity to ¹³C-UBT and with a histological diagnosis of *H. pylori*-related gastritis with/without PGC.

Exclusion criteria were as follows: Past GC or gastric related surgery, impossibility to perform at least five biopsies during endoscopy, relevant comorbidities (cardiac, respiratory, chronic renal insufficiency, chronic liver disease, and psychiatric conditions), anticoagulant therapy/coagulation disorders, non-steroidal anti-inflammatory drugs and/or long-term proton pump inhibitors users, and active smoking habit. Autoimmune co-morbidities were not considered as exclusion criteria.

A history of *H. pylori* infection was investigated on the basis of medical records or a face-to-face clinical examination. During each procedure the qualified endoscopists performed the biopsies according to the study protocol to ascertain or confirm *H. pylori* presence and its related histological alterations. All visible gastric lesions were initially evaluated by HR-WLE with NBI. In detail, we performed at least five random biopsies using HR-WLE with NBI, followed by targeted biopsies on endoscopically evident lesions, suggestive of IM or dysplasia^[28]. Furthermore, at least five different images were acquired during gastroscopy by a single expert observer, who was blind to the final histology, and who predicted the diagnosis of normal mucosa, atrophy, IM, or dysplasia using the EGGIM classification according to Pimentel-Nunes *et al*^[29].

Histopathological characteristics

The histological result was considered as the gold standard for the diagnosis of dysplasia and IM; all gastric biopsy specimens were independently assessed by two expert gastrointestinal pathologists (MLC and RA). The Sydney System, and the

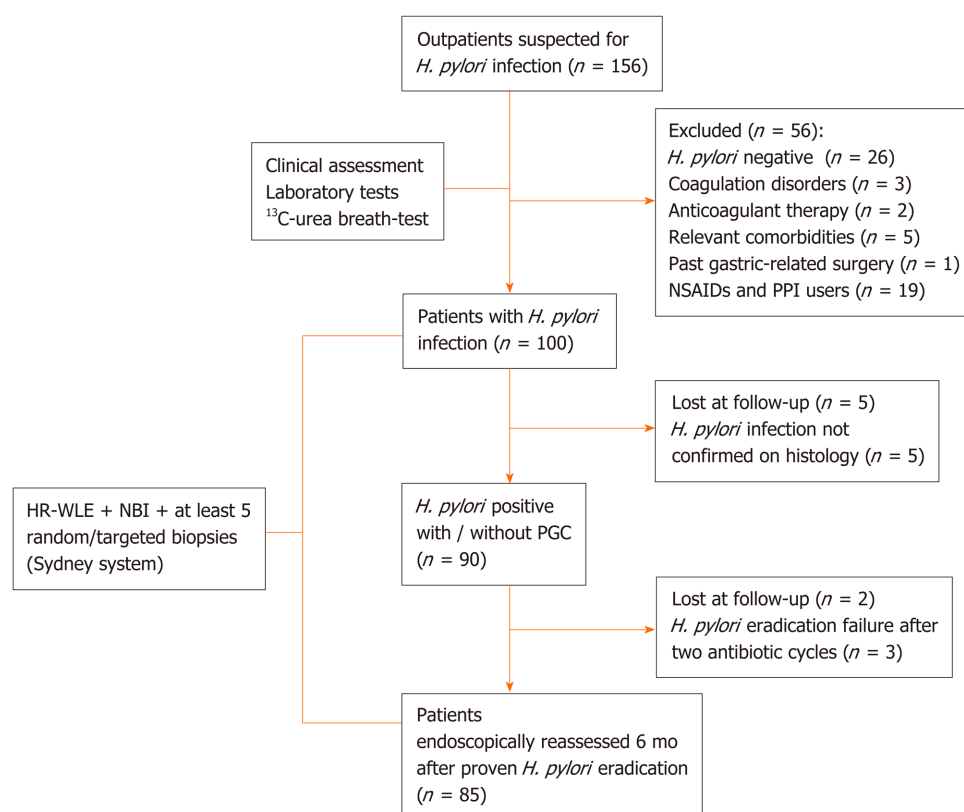


Figure 1 Flow diagram of patient's selection. *H. pylori*: *Helicobacter pylori*; NSAIDs: Non-steroidal anti-inflammatory drugs; PPI: Proton pump inhibitor; HR-WLE: High resolution-white light endoscopy; NBI: Narrow band imaging; PGC: Precancerous gastric conditions.

OLGA and OLGIM systems assessment were used for histological staging of gastritis^[30,31,39]; the following diagnostic categories were considered for the evaluation of dysplasia according to the World Health Organization classification: Negative for intraepithelial neoplasia/dysplasia, indefinite for intraepithelial neoplasia/dysplasia, low-grade intraepithelial neoplasia/dysplasia, high-grade intraepithelial neoplasia/dysplasia and intra-mucosal invasive neoplasia/intra-mucosal carcinoma^[39]. In all patients, *H. pylori* eradication was assessed by a prior negative result of ¹³C-UBT and confirmed by histology.

Statistical analysis

Normal distribution of continuous variables was assessed with the Shapiro-Wilk test and data were expressed as mean and \pm SD. Categorical variables were reported as percentages and compared using the χ^2 test or Fisher's exact test, when needed. The probability of detecting gastric dysplasia after *H. pylori* eradication was evaluated using univariate and multivariate logistic regression analyses. The association between each explanatory variable and the outcome (detection of dysplasia) was tested using the likelihood ratio test. For each variable included in the multivariate model, we calculated both unadjusted and adjusted odds ratios (OR), with their 95% confidence intervals (CI), and the level of significance (using the likelihood ratio test). Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS 23.0 software (SPSS, Chicago, IL, United States) and R version 3.4.3 (<http://www.R-project.org/>).

RESULTS

The clinical characteristics of the 85 enrolled patients are described in Table 1. At baseline, the majority of patients (71.8%) had an extensive endoscopic atrophic gastritis (pan-atrophy, corpus-predominant or antrum-predominant atrophy), and the minority (22.4%) had focal antrum atrophy (Table 2)^[32]. The patients with a less advanced degree (0-2 and 3-4) of the EGGIM scale were 80%; histological gastritis was

Table 1 Baseline demographic and clinical characteristics of patients who underwent *Helicobacter pylori* eradication

Parameters	Patients (n = 85)
Age, mean (SD), yr	56.1 (12.3)
Gender, n (%)	
Female	53 (62.4)
BMI, mean (SD), kg/m ²	25.1 (2.2)
Alcohol users (12-24 g/dL / die), n (%)	27 (31.8)
Previous smokers, n (%)	12 (14.1)
Drug users, n (%)	23 (27.1)
Family history of gastric cancer, n (%)	4 (4.7)
Family history of other cancer, n (%)	9 (10.6)
Autoimmune comorbidity	
Autoimmune atrophic gastritis	12 (14.1)
Autoimmune thyroiditis	6 (7.1)
Type-1/2 diabetes mellitus	3 (3.5)
Skin psoriasis	1 (1.2)
Rheumatoid arthritis	1 (1.2)
Sjögren syndrome	1 (1.2)
A. thyroiditis + vitiligo	1 (1.2)
A. thyroiditis + Crohn's disease	1 (1.2)
A. thyroiditis + Sjögren syndrome	1 (1.2)
APCA and/or AIF antibody positivity	12 (14.1)
Endoscopy indication, n (%)	
Gastroesophageal reflux	17 (20)
Recurrent abdominal pain	12 (14.1)
Dyspepsia	41 (48.2)
Unexplained anemia	15 (17.7)
<i>H. pylori</i> eradication scheme, n (%)	
Quadruple ¹	53 (62.4)
Modified triple ²	28 (32.9)
Triple ³	3 (3.6)
Sequential ⁴	1 (1.2)
<i>H. pylori</i> eradication cycles, n (%)	
One-cycle	71 (83.5)
Two-cycles	14 (16.5)

Data are expressed as number of patients and percentage (in parenthesis).

¹Bismuth + Metronidazole + Tetracycline + Proton pump inhibitor.

²Amoxicillin + Levofloxacin + Proton pump inhibitor.

³Amoxicillin + Clarithromycin + Proton pump inhibitor.

⁴Amoxicillin + Clarithromycin + Proton pump inhibitor Amoxicillin (5 d), then Clarithromycin + Metronidazole (5 d) + Proton pump inhibitor. BMI: Body mass index; SD: Standard deviation; APCA: Anti-parietal cell antibody; AIF: Anti-intrinsic factor; *H. pylori*: *Helicobacter pylori*; PPI: Proton pump inhibitor.

moderate/severe and mild in 77.6% and 22.4% of the patients respectively; 45.8% of patients also had mucosal associated lymphoid tissue (MALT) hyperplasia (Table 2). Fifteen patients (17.6%) had LGD on random biopsies. Among the 49 patients with

Table 2 Endoscopic and histological characteristics of patients before and after *Helicobacter pylori* eradication

Parameters	Before <i>H. pylori</i> eradication (n = 85)	After <i>H. pylori</i> eradication (n = 85)	P value
Endoscopic atrophy ¹ , n (%)			
Absent	5 (5.9)	4 (4.7)	1.0
Antrum	19 (22.4)	19 (22.4)	1.0
Antrum-predominant	18 (21.2)	12 (14.1)	0.23
Corpus-predominant	21 (24.7)	23 (27.1)	0.73
Pan-atrophy	22 (25.9)	27 (31.8)	0.40
OLGA-scale, n (%)			
Stage 0	4 (4.7)	4 (4.7)	1.0
Stage 1	22 (25.9)	28 (32.9)	0.31
Stage 2	34 (40)	23 (27.1)	0.07
Stage 3	20 (23.5)	25 (29.4)	0.38
Stage 4	5 (5.9)	5 (5.9)	1.0
EGGIM-scale, n (%)			
0-2	47 (55.3)	45 (52.9)	0.76
3-4	21 (24.7)	10 (11.8)	0.03 ^a
5-6	12 (14.1)	21 (24.7)	0.08
7-8	4 (4.7)	4 (4.7)	1.0
9-10	1 (1.2)	5 (5.9)	0.21
OLGIM-scale, n (%)			
Stage 0	40 (47.1)	29 (34.1)	0.08
Stage 1	14 (16.5)	17 (20)	0.55
Stage 2	14 (16.5)	14 (16.5)	1.0
Stage 3	13 (15.3)	18 (21.2)	0.32
Stage 4	4 (4.7)	7 (8.2)	0.53
Gastritis at histology ² , n (%)			
Quiescent	0	81 (95.3)	< 0.0001 ^b
Mild	19 (22.4)	4 (4.7)	0.001 ^b
Moderate	46 (54.1)	0	< 0.0001 ^b
Severe	20 (23.5)	0	< 0.0001 ^b
MALT-hyperplasia, n (%)			
Absent	46 (54.1)	82 (96.5)	< 0.0001 ^b
Mild	25 (29.4)	3 (3.5)	< 0.0001 ^b
Moderate	11 (12.9)	0	0.007 ^b
Severe	3 (3.5)	0	0.24
Histological LGD ³ , n (%)			
Absent	70 (82.4)	57 (67.1)	0.02 ^a
On random biopsies	15 (17.6)	9 (10.6)	0.19
On random + on lesions biopsies	0	6 (7)	0.03 ^b
Only on visible lesions	0	13 (15.3)	0.0001 ^b

Data are expressed as number of patients and percentage (in parenthesis).

¹By Kimura and Takemoto^[32].²By Sydney System.³LGD: Low-grade dysplasia according to World Health Organization classification.^aBy χ^2 test.^bby Fisher's exact test. *H. pylori*: *Helicobacter pylori*; EGGIM: Endoscopic grading of gastric intestinal metaplasia; MALT: Mucosa-associated lymphoid tissue; OLGA: Operative Link on Gastritis Assessment; OLGIM: Operative Link on Gastric Intestinal Metaplasia.

histological pan-atrophy or corpus-predominant atrophy, 11 (22.4%) tested positive for APCA and/or for AIF antibodies. In 100% of the cases the histological mononuclear and polymorphonuclear cell infiltration disappeared or decreased after *H. pylori* eradication. Additionally, the proportion of patients with mild and moderate/severe grades of MALT hyperplasia significantly decreased after *H. pylori* eradication (29.4% vs 3.5%, $P < 0.001$ and 16.4% vs 0%, $P < 0.001$, respectively; **Table 2**). Nevertheless, the proportion of OLGA, OLGIM stages, and that of patients with histological diagnosis of LGD on random biopsies did not significantly change after *H. pylori* eradication (17.6% vs 10.6%, $P = 0.19$) (**Table 2** and **Figure 2**). The detection of LGD on visible lesions significantly increased after *H. pylori* eradication (0% vs 22.3%, $P < 0.001$; **Table 2**). Among the 9 patients who showed LGD on random biopsies after *H. pylori* eradication, only 2 (22.2%) had already had a diagnosis of LGD on random biopsies before *H. pylori* eradication. Among the 6 patients with LGD on random and visible lesion biopsies after *H. pylori* eradication, two (33.3%) were negative for LGD before eradication. Furthermore, the proportion of the 13 patients with a new diagnosis of LGD only on visible lesions was significantly higher after *H. pylori* disappearance (0% vs 15.3%, $P < 0.001$) and in 6 of them (46.1%) LGD was not detected before *H. pylori* eradication.

The characteristics of the 19 subjects in whom LGD was detected on visible lesions after *H. pylori* eradication are shown in **Supplementary Table 1**. In details, 11 subjects (57.9%) were male, and in 8 patients (42.1%) LGD was missed before *H. pylori* eradication. Five patients (26.3%) had APCA and/or AIF positivity. Comparison of the patients with or without LGD ($n = 28$ vs $n = 57$ respectively) after *H. pylori* eradication is shown in **Table 3**. In patients with LGD, the age was older (60.9 ± 8.2 vs 53.7 ± 13.4 years, $P = 0.01$), there were more alcohol users or past smokers (53.6% vs 21.1%, $P = 0.002$ and 35.7% vs 3.5%, $P < 0.001$, respectively), there was a higher proportion of APCA and/or AIF antibody positivity (28.6% vs 7%, $P = 0.02$), there were more familial cases of GC (14.3% vs 0%, $P < 0.001$) and more advanced stages of OLGA and OLGIM, both at the baseline and after *H. pylori* eradication ($P < 0.001$ for both). When we compared the histological characteristics of the 28 patients with LGD after *H. pylori* eradication, we observed that the moderate/severe grades of gastritis and MALT hyperplasia significantly regressed during surveillance ($P < 0.001$ and $P = 0.004$, respectively), whereas OLGA stages were similar ($P = 0.76$; **Supplementary Table 2**). A higher prevalence of OLGIM stages 3-4 was observed after *H. pylori* eradication, but it did not reach the level of statistical significance (57.1% vs 75%, $P = 0.16$).

As shown in **Supplementary Table 3**, in patients without LGD after *H. pylori* eradication only gastritis significantly improved at the follow-up endoscopy ($P < 0.001$). **Table 4** shows the results of the linear regression analysis. According to the multivariate analysis adjusted for age, alcohol use, MALT hyperplasia regression/reduction and for APCA and/or AIF antibody presence, the probability for detecting gastric LGD, randomly or on visible lesions after eradication of *H. pylori*, was significantly higher in patients with regression/reduction of MALT hyperplasia (OR = 3.10, 95%CI: 1.05-9.12, $P = 0.04$), alcohol consumption (OR = 3.88, 95%CI: 1.31-11.49, $P = 0.01$), and APCA and/or AIF antibody positivity (OR = 5.47, 95%CI: 1.33-22.39, $P < 0.04$).

DISCUSSION

Our study shows that HR-WLE in combination with NBI can diagnose gastric LGD on visible lesions with the highest accuracy after regression of *H. pylori*-induced signs of active infection (**Figure 3** and **4**). This suggests that, in high-risk subjects without alarm features for malignancy, non-invasive tests should be used for prior *H. pylori* identification, and a high-quality upper endoscopy to identify dysplastic lesions should be postponed after *H. pylori* eradication has been achieved. This strategy could

Table 3 Demographic and clinical characteristics of patients with low-grade dysplasia detected on visible gastric lesions or randomly and without low-grade dysplasia, before and after *Helicobacter pylori* eradication

Parameters	With LGD (n = 28)	Without LGD (n = 57)	P value
Age, mean (SD), yr	60.9 (8.2)	53.7 (13.4)	0.01 ^a
Gender, n (%)			
Female	15 (53.6)	38 (66.7)	0.24
BMI, mean (SD), kg/m ²	25 (2.4)	25 (2.3)	1.0
Alcohol users (12-24 g/dL/die), n (%)	15 (53.6)	12 (21.1)	0.002 ^b
Previous smokers, n (%)	10 (35.7)	2 (3.5)	< 0.0001 ^c
Family history of gastric cancer, n (%)	4 (14.3)	0	0.001 ^c
Family history of other cancer, n (%)	6 (21.4)	3 (5.3)	0.001 ^c
Autoimmune comorbidity			
Autoimmune atrophic gastritis	8 (28.6)	4 (7)	0.02 ^c
Autoimmune thyroiditis	3 (10.7)	3 (5.3)	0.39
A. thyroiditis + vitiligo	1 (3.6)	0	0.33
A. thyroiditis + Crohn's disease	1 (3.6)	0	0.33
A. thyroiditis + Sjögren syndrome	0	1 (1.7)	1.0
Sjögren syndrome	0	1 (1.7)	1.0
Type-1/2 diabetes mellitus	1 (3.6)	2 (3.5)	1.0
Skin psoriasis	1 (3.6)	0	0.33
Rheumatoid arthritis	0	1 (1.7)	1.0
APCA and/or AIF antibody positivity	8 (28.6)	4 (7)	0.02 ^c
<i>H. pylori</i> eradication scheme, n (%)			
Quadruple ¹	17 (60.7)	36 (63.2)	0.82
Modified triple ²	9 (32.1)	19 (33.3)	0.91
Triple ³	1 (3.6)	2 (3.5)	1.0
Sequential ⁴	1 (3.6)	0	0.33
<i>H. pylori</i> eradication cycles, n (%)			
One cycle	22 (78.6)	46 (86)	0.82
Two cycles	6 (21.4)	8 (14)	0.82
OLGA scale before ⁵			
Stage 0	0	4 (7)	0.3
Stage 1-2	8 (28.6)	48 (84.2)	< 0.0001 ^b
Stage 3-4	20 (71.4)	5 (8.8)	< 0.0001 ^c
OLGA scale after ⁶			
Stage 0	0	4 (7)	0.3
Stage 1-2	7 (25)	44 (77.2)	< 0.0001 ^b
Stage 3-4	21 (75)	9 (15.8)	< 0.0001 ^b
OLGIM scale before			
Stage 0	0	40 (70.1)	< 0.0001 ^c
Stage 1-2	12 (42.8)	16 (28.1)	0.17
Stage 3-4	16 (57.1)	1 (1.8)	< 0.0001 ^c
OLGIM scale after			

Stage 0	0	29 (50.9)	< 0.0001 ^c
Stage 1-2	7 (25)	24 (42.1)	0.12
Stage 3-4	21 (75)	4 (7)	< 0.0001 ^c
Gastritis at histology before, <i>n</i> (%)			
Quiescent	0	0	1.0
Mild	3 (10.7)	16 (28.1)	0.10
Moderate-severe	25 (89.3)	41 (71.9)	0.10
Gastritis at histology after, <i>n</i> (%)			
Quiescent	26 (92.9)	55 (96.5)	0.59
Mild	2 (7.1)	2 (3.5)	0.50
Moderate-severe	0	0	1.0
MALT hyperplasia before, <i>n</i> (%)			
Absent	10 (35.7)	36 (63.2)	0.02 ^b
Mild	10 (35.7)	15 (26.3)	0.37
Moderate	6 (21.4)	5 (8.8)	0.17
Severe	2 (7.2)	1 (1.8)	0.25
MALT hyperplasia after, <i>n</i> (%)			
Absent	10 (35.7)	36 (63.2)	0.02 ^b
Mild	18 (64.3)	21 (36.8)	0.02 ^b
Moderate	0	0	1.0
Severe	0	0	1.0

Data are expressed as number of patients and percentage (in parenthesis).

¹Bismuth + Metronidazole + Tetracycline + Proton pump inhibitor.

²Amoxicillin + Levofloxacin + Proton pump inhibitor.

³Amoxicillin + Clarithromycin + Proton pump inhibitor.

⁴Amoxicillin + Clarithromycin + Proton pump inhibitor Amoxicillin (5 d), then Clarithromycin + Metronidazole (5 d) + Proton pump inhibitor.

⁵Before *Helicobacter pylori* eradication (by Sydney System).

⁶After *Helicobacter pylori* eradication.

^aBy *t*-test.

^bBy χ^2 test.

^cBy Fisher's exact test. BMI: Body mass index; SD: Standard deviation; APCA: Anti-parietal cell antibody; AIF: Anti-intrinsic factor; *H. pylori*: *Helicobacter pylori*; PPI: Proton pump inhibitor; OLGA: Operative Link on Gastritis Assessment; OLGIM: Operative Link on Gastric Intestinal Metaplasia; MALT: Mucosa-associated lymphoid tissue.

be useful for yielding a higher dysplasia detection rate and for better defining cancer risk and surveillance time.

Despite conflicting evidence, *H. pylori* eradication is presently advised in high-risk subjects for its potential to reduce GC incidence and induce regression of inflammation and atrophic gastritis^[7,22-27,40]. Originally, the use of WLE alone provided a weak association between endoscopic and histological findings in diagnosing PGC, probably due to the inefficient technology of endoscopy imaging^[41-43]; recent studies have instead shown that the use of HR-WLE allows for a high concordance accuracy for this purpose^[7,36]. There is strong evidence that virtual chromoendoscopy should be used for the diagnosis of PGC because of its better performance compared to HR-WLE^[34-37,44]. Capelle *et al*^[33] studied high-risk patients with IM or dysplasia undergoing endoscopic surveillance 2.0 years (range 0.8–21.1) and 1.9 years (range 0.2–5.2) respectively after the initial diagnosis and showed a slightly better diagnostic yield for the detection of advanced PGC using HRE with NBI *vs* HR-WLE^[33]. Conventional CE with the application of dyes has been associated with the highest PGC detection accuracy as compared to virtual chromoendoscopy although procedural time is considerably longer^[45-47]. As a result of such evidence, the updated version of the European guidelines suggests that a high-quality endoscopy requires the use of NBI^[7].

Table 4 Probability of detecting low-grade dysplasia randomly or on visible lesions after *Helicobacter pylori* eradication

Variable	Univariate		Multivariate	
	OR (95% CI)	P value	OR ¹ (95%CI)	P value
Age, yr	1.05 (1.01-1.11)	< 0.02	1.05 (1.00-1.10)	0.07
Gender				
Female	1.00 ²		-	
Male	1.73 (0.69-4.37)	0.24	-	-
BMI, kg/m ²	0.93 (0.75-1.15)	0.49	-	-
Alcohol use				
No	1.00 ²		1.00 ²	
Yes	4.33 (1.63-11.51)	< 0.01	3.88 (1.31-11.49)	0.01
Drug use				
No	1.00 ²		-	
Yes	1.45 (0.54-3.94)	0.46	-	-
MALT hyperplasia regression/reduction				
No	1.00 ²		-	
Yes	3.90 (1.20-7.91)	< 0.02	3.10 (1.05-9.12)	0.04
APCA and/or AIF antibody positivity				
No	1.00 ²			
Yes	5.30 (1.44-19.56)	0.01	5.47 (1.33-22.39)	< 0.02

¹Adjusted for age, alcohol use, Mucosa-associated lymphoid tissue hyperplasia reduction/regression and anti-parietal cell antibody and/or anti-intrinsic factor antibody positivity.

²Reference group. LGD: Low-grade dysplasia; *H. pylori*: *Helicobacter pylori*; OR: Odds ratio; BMI: Body mass index; MALT: Mucosa-associated lymphoid tissue; APCA: Anti-parietal cell antibody; AIF: Anti-intrinsic factor.

In our study, the histological signs of active gastritis and MALT hyperplasia disappeared or decreased in 100% and 96.5% of patients with or without PGC after *H. pylori* eradication, respectively. The overall prevalence of LGD on random biopsies at a 6-mo interval was similar (17.6% *vs* 10.6%). Nevertheless, among the patients with newly diagnosed LGD on visible lesions, the percentage of endoscopically missed dysplasia was 42.1% before *H. pylori* eradication, when active gastritis was present. Unexpectedly, at the baseline 26.3% of such patients (5/19) had an overlapping AAG with APCA and/or AIF positivity. This prevalence rose to 28.6% (8/28 patients) when we considered the total patients with dysplasia, and the percentage of this positivity did not change after *H. pylori* eradication ($P = 1.0$, data not shown). We observed an almost doubled prevalence of gastric LGD on biopsies performed randomly or on visible lesions before and after *H. pylori* disappearance (17.6% *vs* 32.9% respectively). A similar prevalence was found in another study from two referral centers using NBI endoscopy, in which dysplasia was detected in 28/85 (33%) and 38/85 *H. pylori* positive patients (45%)^[37].

Patients with LGD were older and showed more advanced OLGA and OLGIM stages as compared to those without LGD, at baseline as well as after *H. pylori* eradication. The prevalence of OLGIM stages 3-4 showed a tendency to increase after *H. pylori* eradication only in patients with dysplasia, from 57.1% to 75%.

The higher prevalence of LGD after *H. pylori* eradication could depend on the presence of more severe and extensive mucosal atrophy and IM at baseline in our high-risk subgroup of patients rather than disease progression itself, considering the short interval of endoscopic surveillance of our study. In this scenario, the background of active *H. pylori* inflammation is likely to play a confounding role that may have hampered the accurate detection of gastric dysplasia. Nevertheless, the unexpected high baseline prevalence of dysplasia may be partially justified by the concomitant presence of AAG in a considerable number of our patients, in accordance with results from a recent study showing that in the presence of AAG the risk of developing more

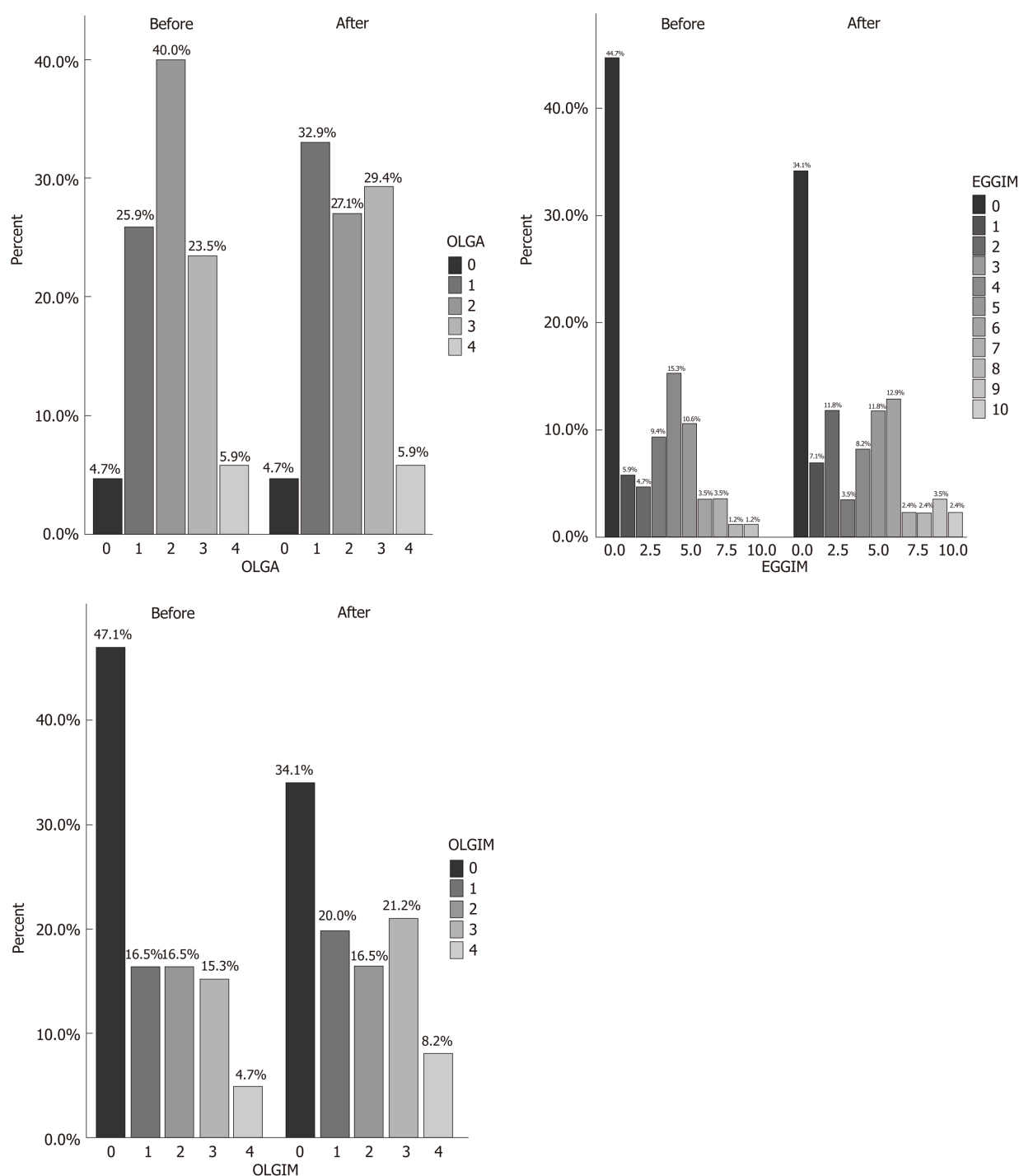


Figure 2 Prevalence of Operative Link on Gastritis Assessment, endoscopic grading of gastric intestinal metaplasia, and Operative Link on Gastric Intestinal Metaplasia scores, respectively in the 85 patients before and after *Helicobacter pylori* eradication. OLGA: Operative Link on Gastritis Assessment; EGGIM: Endoscopic grading of gastric intestinal metaplasia; OLGIM: Operative Link on Gastric Intestinal Metaplasia.

advanced stages on long-term follow-up is greater in patients with more severe gastric lesions^[8]. The overlap between autoimmune and *H. pylori*-induced chronic gastritis may presumably be associated with a more severe gastric injury, especially in older subjects.

At a multivariate analysis, the probability for detecting gastric dysplasia after resolution of *H. pylori*-related active inflammation was significantly higher in older patients with regression or reduction of MALT hyperplasia, greater alcohol consumption, and APCA and/or AIF positivity. Therefore, MALT hyperplasia with active gastritis, whether induced or not by *H. pylori*, could be an additional confounding factor influencing the detection of PGC, and, particularly, LGD in high-risk patients (Table 4).



Figure 3 Gastric white-light endoscopy, narrow band imaging and histological evaluation before *Helicobacter pylori* eradication. A, B: Gastritis during white-light endoscopy and narrow band imaging assessment of corpus before *Helicobacter pylori* eradication; and C: Histological evaluation: moderately atrophic chronically active gastritis with lymphoplasmacellular infiltration of the lamina propria and foveolar epithelium hyperplasia (fundus before *Helicobacter pylori* eradication). Sections of 3 microns colored with Hematoxylin Eosin and Giemsa respectively. Magnifications: $\times 10$.

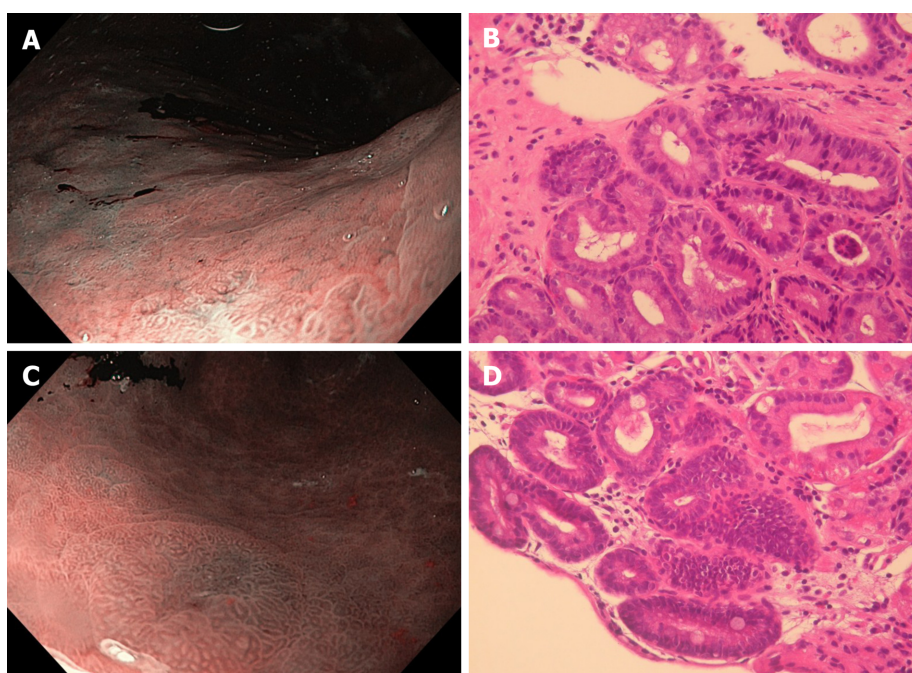


Figure 4 Gastric narrow band imaging and histological evaluation after *Helicobacter pylori* eradication. A: Low-grade dysplasia on flat lesion during narrow band imaging assessment of corpus after *Helicobacter pylori* eradication; B: Histological appearance: inactive chronically mild atrophic gastritis with intestinal metaplasia and low-grade dysplasia on intestinal metaplastic epithelium (fundus after *Helicobacter pylori* eradication); C: Low-grade dysplasia aspect of antrum on visible lesion during narrow band imaging assessment after *Helicobacter pylori* eradication; and D: Histological appearance: inactive chronically moderate atrophic gastritis with intestinal metaplasia and low-grade dysplasia on intestinal metaplastic epithelium (antrum after *Helicobacter pylori* eradication). Hematoxylin Eosin. Sections of 3 microns. Magnification: $\times 10$.

The prevalence of autoimmune diseases (24.7%) in our patients showed a tendency to increase among patients with LGD (35.7% *vs* 17.5% in those without LGD, $P = 0.06$ by χ^2 test). Since autoimmune disorders are linked to the presence of DRB1 and DQB1 haplotypes our finding may suggest a reciprocal role between the genetics of immune response and *H. pylori* chronic infection.

Our results are in full accordance with the current European recommendations, which suggest to perform an endoscopic reassessment with HRE-NBI as soon as possible after dysplasia is diagnosed in the “apparent” absence of endoscopically visible lesions, to search for malignancy on misdiagnosed lesions^[7,27,48]. Where the presence of *H. pylori* active gastritis without alarming features for malignancy is suspected, considering the present lack of clinical recommendations on the diagnosis and surveillance of PGC^[7], our study suggests that the best diagnostic workout in symptomatic patients should entail performing prior *H. pylori* non-invasive tests, thus increasing the probability of detecting LGD on visible lesions at an endoscopy carried

out soon after *H. pylori* eradication has been achieved.

There are some limitations to our study. The sample size is relatively small, although all endoscopies were performed in a standardized way by using the same biopsy protocol and technical procedures and with the presence of the same endoscopist throughout the study. The hypothesis that LGD could have progressed into visible lesions is unlikely due to our short 6-mo follow-up interval^[7]. The risk of PGC progression has indeed been demonstrated to increase only on long-term follow-up (2-16 years), after eradication of *H. pylori*^[22-25,40]. Our results may help explain the heterogeneous findings of a possible increased PGC prevalence after *H. pylori* eradication in long-term surveillance studies, as this might be due to a misdiagnosis at initial endoscopic examination.

In conclusion, HR-WLE with NBI can be more accurate in diagnosing LGD on visible lesions after *H. pylori* eradication has been achieved, probably due to the disappearance of the underlying confounding effects of inflammatory and mucosal lymphoproliferative changes induced by *H. pylori* chronic active infection. Elderly patients and those with autoimmune diseases could be at higher risk for *H. pylori* chronic infection. An effective and cost-effective strategy to diagnose LGD with the highest accuracy should entail a high-quality upper endoscopy performed soon after eradication of *H. pylori* infection, detected by prior non-invasive tests.

ARTICLE HIGHLIGHTS

Research background

Helicobacter pylori (*H. pylori*) infection is frequently responsible for precancerous gastric conditions (PGC) and the long-term risk of PGC may even progress after *H. pylori* eradication.

Research motivation

Heterogeneous long-term endoscopic follow-up studies (2-16 years) have shown conflicting results on the efficacy of *H. pylori* eradication in reducing the prevalence and histological progression of advanced PGC. Moreover, High-Resolution White-Light Endoscopy (HR-WLE) in combination with narrow-band imaging (NBI) is effective in detecting PGC and determines the timing and mode of endoscopic surveillance.

Research objectives

To assess the efficacy of HR-WLE with NBI in detecting PGC, before and after *H. pylori* eradication at a short-term interval.

Research methods

We evaluated 85 consecutive patients with *H. pylori*-related gastritis with/without PGC at baseline and 6 mo after proven *H. pylori* eradication. The Operative-Link on Gastritis-Assessment and Operative-Link on Gastric-Intestinal Metaplasia have been used as gold standards for histological definition of gastritis, atrophy and intestinal metaplasia. Serum anti-parietal cell antibody and anti-intrinsic factor were measured when autoimmune atrophic gastritis was suspected.

Research results

HR-WLE in combination with NBI allows for a more accurate diagnosis of gastric low-grade dysplasia (LGD) when performed soon after *H. pylori* eradication, due to regression of *H. pylori*-induced signs of inflammation. Furthermore, we observed an unexpected high prevalence of autoimmune disorders, suggesting an interaction between the genetics of immune response and *H. pylori* chronic infection, especially in relation to the risk of LGD development.

Research conclusions

HR-WLE with NBI allows an accurate diagnosis of gastric LGD on visible lesions after regression of *H. pylori*-induced signs of active infection, especially in high-risk subjects. Patients with overlap between autoimmune and *H. pylori*-induced chronic gastritis may require more extensive gastric mapping.

Research perspectives

Our findings will appeal to both clinical gastroenterologists and endoscopists, and stimulate the development of more accurate and cost-effective strategies for identifying patients with *H. pylori* infection who are at risk of gastric cancer. Subjects with an overlap between autoimmune and *H. pylori*-induced chronic gastritis should be considered to be at a higher risk of more severe gastric injury.

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