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RESEARCH ARTICLE



Gastric dysplasia in random biopsies: the influence of *Helicobacter pylori* infection and alcohol consumption in the presence of a lesion

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ABSTRACT

Background: Gastric dysplasia in the absence of an endoscopically defined lesion is rare, usually either a false positive diagnosis or a previously unidentified precancerous lesion during esophagogastroduodenoscopy (EGD).

Aims: Evaluate factors associated with the presence of an endoscopically visible lesion during follow-up in patients with histologic diagnosis of gastric dysplasia in random biopsies.

Methods: Retrospective cohort study including patients referred to our institution for gastric dysplasia in random biopsies during Index EGD. Endoscopic evaluation was performed with a high-definition endoscope using narrow band imaging (HD EGD-0). If no lesion was detected, endoscopic surveillance (HD EGD-FU) was conducted within 6 months for high grade dysplasia (HGD) or 12 months for low grade (LGD) or indefinite for dysplasia (IFD).

Results: From a total sample of 96 patients, 5 (5.2%) presented with an endoscopically visible lesion during HD EGD-0, while 10 lesions (10.4%) were identified during HD EGD-FU. Patients with *Helicobacter pylori* infection at Index EDG and with regular alcohol consumption (≥ 25 g/day) were 8 and 4 times more likely to have an endoscopically visible lesion on HD EGD-FU ($p=0.012$ and $p=0.047$). In binary logistic regression, both factors were independent predictors of the presence of gastric lesion on HD EGD-FU (OR 9.284, $p=0.009$ and OR 5.025, $p=0.033$).

Conclusions: The presence of an endoscopically visible lesion after the histologic diagnosis of gastric dysplasia in random biopsies was more frequent during HD EGD-FU. *H. pylori* infection at Index EGD and regular alcohol consumption were significant predictors of the presence of gastric lesion on HD EGD-FU.

Abbreviations: CAG: Chronic atrophic gastritis; CE: Chromoendoscopy; EGC: Early gastric cancer; EGD: Esophagogastroduodenoscopy; EMR: Endoscopic mucosal removal; ESD: Endoscopic submucosal dissection; GC: Gastric cancer; HD EGD-0: High-definition esophagogastroduodenoscopy (initial); HD EGD-FU: High-definition esophagogastroduodenoscopy (follow-up); HD-WLE: High-definition white-light endoscopy; HGD: High grade dysplasia; IFD: Indefinite for dysplasia; IQR: Interquartile range; IM: Intestinal metaplasia; LGD: Low grade dysplasia; ME-NBI: Magnifying endoscopy with NBI; NBI: Narrow-band imaging; NSAIDs: Nonsteroidal anti-inflammatory drugs; PPI: Proton-pump inhibitors; SD: Standard deviation; WLE: White-light endoscopy

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Gastric dysplasia; random gastric biopsies; *Helicobacter pylori*; alcohol drinking

Introduction

Gastric cancer (GC) is one of the leading causes of cancer-related deaths worldwide [1–3]. Although most cases are diagnosed at an advanced stage, early recognition and treatment is possible, and screening and surveillance of people at risk may decrease gastric cancer mortality [2, 3]. Early gastric cancer (EGC) has an excellent prognosis with a 5-year survival rate of 92.6% after endoscopic resection [4], whereas GC diagnosed at a late stage has a 5-year survival rate of less than 30% [5].

Non-cardia GC is usually developed through a series of mucosal changes from chronic atrophic gastritis (CAG), intestinal metaplasia (IM), dysplasia and adenocarcinoma [1, 2]. Thus, CAG and IM are independent risk factors for the development

of non-hereditary intestinal-type gastric adenocarcinoma, especially when affecting both antral and corpus mucosae [2, 4]. The structural changes observed in gastric mucosal atrophy are loss of resident glands with replacement by metaplastic glandular units, as well as the presence of lymphocytes and plasma cells. IM is characterized by the presence of mucin-producing goblet cells and Paneth cells. These metaplastic glands are prone to de-differentiation, and dysplasia is defined as neoplastic epithelia that lacks the capacity of invasion [3, 5]. Dysplasia is classified as low- or high-grade, depending on the architectural and cellular atypia [5].

Gastric dysplasia is a direct neoplastic precancerous lesion [2]. The risk of malignant progression increases with the

histological grade of the dysplasia, with high-grade dysplasia (HGD) having a ten-fold higher risk of progression to carcinoma or presence of synchronous carcinoma. However, it is important to highlight that both low-grade dysplasia (LGD) and HGD have the potential to progress to carcinoma [6, 7]. In fact, endoscopic biopsies are insufficient for correct diagnosis of visible lesions, and the identification of LGD or indefinite for dysplasia (IFD) on biopsy of a visible lesion can be already a malignant lesion [2, 8]. Predictive characteristics for a histologic upstaging of LGD after endoscopic resection include a larger size, depressed type, and surface appearance with erythema, ulcer, or erosion [6].

Helicobacter pylori infection is considered a major risk factor for the development of GC. Other factors of lesser importance include family history, smoking, and increased consumption of dietary salt [5]. *H. pylori* eradication might prevent or delay carcinogenesis, having the greatest benefit in patients with atrophic chronic gastritis [2, 9]. Patients with IM and extensive atrophy, however, are at increased risk of GC development even after *H. pylori* eradication [10].

High-definition endoscopy with chromoendoscopy (CE), especially using narrow-band imaging (NBI), has been proven to be better than high-definition white-light endoscopy (HD-WLE) in identifying metaplastic or dysplastic changes and guiding biopsies [2]. CE is recommended for the diagnosis of gastric precancerous conditions [2, 6]. The index esophagogastroduodenoscopy (EGD) should include gastric biopsies for adequate identification of gastric precancerous conditions and *H. pylori* infection diagnosis. Biopsies should be taken from at least two topographic sites, antrum, and corpus, and labelled in two separate vials, as well as any visible neoplastic suspicious lesions on a separate vial [2, 4, 11]. In fact, CE-targeted biopsies and mapping biopsies are the best way of detecting most cases of advanced gastritis [2].

Patients with an endoscopically visible lesion harboring LGD, HGD or carcinoma should undergo staging and treatment [2].

The presence of gastric dysplasia in the absence of an endoscopically defined lesion is rare and when histologic diagnosis of gastric dysplasia is established in such situations, it is usually either a false positive result or a lesion not adequately identified in the index EGD. If no lesion is detected, biopsies for staging of gastritis (if not previously done) and endoscopic surveillance within 6 months (if HGD) to 12 months (if LGD or IFD) are recommended. If a lesion is identified and the endoscopic assessment suggests dysplasia, resection is recommended without the need for further sampling [2, 12].

Most of these patients will not have an endoscopically defined lesion identified during follow-up and the diagnosis of gastric dysplasia in random gastric biopsies represents a misdiagnosis that will lead to unnecessary medical procedures and patients' anxiety. The correct diagnosis, management and follow-up of these patients is important, not only for early detection of dysplastic lesions, but also to avoid over-staging and excessive endoscopic evaluations.

The aim of this study was therefore to evaluate patients with a histological diagnosis of gastric dysplasia in random biopsies, despite no lesion being identified, and find those who had an endoscopically visible lesion identified during

follow-up and which are the factors associated with the presence of a lesion.

Methods

Study design and population

A retrospective, unicentric cohort study was conducted in a university affiliated hospital, including consecutive adult patients who underwent EGD during a 2-year period, following the histologic diagnosis of gastric dysplasia in random gastric biopsies at Index EGD. Patients with an endoscopically visible lesion harboring dysplasia or carcinoma at Index EGD and that lost medical and endoscopic follow-up were not included.

Our protocol

Patients were referred to our institution from primary care units, after undergoing EGD in an outpatient clinic (Index EGD) and having a histologic diagnosis of gastric dysplasia in random gastric biopsies, including IFD, LGD and HGD. In the outpatient clinic, in Index EGD, gastric biopsies were taken according to ESGE guidelines and Sydney protocol [13], obtaining two biopsies from the antrum and two from the corpus in all patients with suspected *H. pylori* infection and for gastritis staging.

After an initial medical appointment, a second endoscopic evaluation was performed immediately in our institution with CE using NBI, the HD EGD-0, to identify any endoscopically visible lesion. If no lesion was detected, endoscopic surveillance was conducted within 6 months (if HGD) or 12 months (if LGD or IFD), the HD EGD-FU. If any lesion was identified and the endoscopic assessment with NBI suggested dysplasia, resection was scheduled. In patients without an endoscopically identified lesion in both HD EGD-0 and HD EGD-FU, biopsies were performed according to the Sydney protocol for staging of gastritis and define future surveillance in primary care units. *H. pylori* eradication was completed in all patients with confirmed infection, with confirmation of eradication using histology, urea breath test or faecal antigen. The study protocol is illustrated in [Figure 1](#).

All EGD were performed using a GIF-190 HQ Olympus endoscope by three experienced endoscopists (SX, JM and PBC). All patients signed an informed consent before undergoing each EGD. Additionally, our protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee (ethics committee and data protection office statements reference number 30/2023).

Data collection

Clinical, laboratory, and endoscopic data were collected from electronic medical records. Clinical data included patients' demographics (age and gender), comorbidities, such as hypertension, diabetes mellitus, alcohol consumption, smoking history (present and/or past), family history of GC and

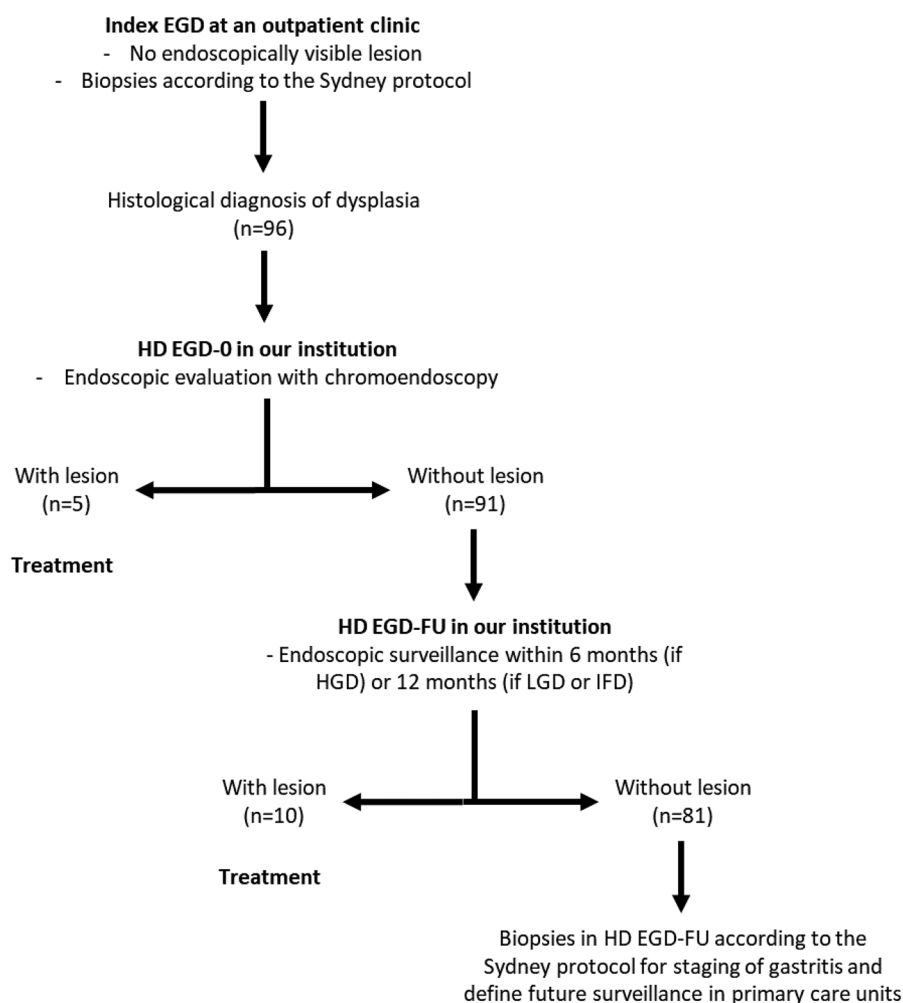


Figure 1. The study protocol.

ongoing medication, namely regular nonsteroidal anti-inflammatory drugs (NSAIDs) use or being medicated with proton-pump inhibitors (PPI). Regular alcohol intake was considered as a consumption of 25 or more grams of alcohol per day, every day. A family history of gastric cancer meant that the patient's family members had gastric cancer within three generations. Other variables included previous *H. pylori* infection, the grade of dysplasia at Index EGD (IFD, LGD or HGD) and location of the biopsies with dysplasia (corpus or antrum). The primary endpoints evaluated included the presence of an endoscopically visible lesion on the HD EGD-0 or the HD EGD-FU, its location, Paris classification and size. The secondary endpoints were the need for endoscopic or surgical treatment, and the final histologic results of the resected lesion.

Statistical analysis

Categorical variables were described as frequencies and percentages, and continuous variables as mean and standard deviation (SD) if normally distributed, or as median and interquartile range (IQR) if not normally distributed. Means and medians of continuous variables were compared using independent group *T* tests or Mann–Whitney *U* test, respectively.

Comparison of categorical variables was performed using the Chi-squared test. A binary logistic regression was performed to evaluate predictors of the presence of gastric lesion during follow-up. A *p* value less than 0.05 was considered statistically significant. Statistical analysis software IBM SPSS version 27.0 (IBM Corp., Armonk, NY, USA) was used for all tests performed.

Results

Baseline characteristics of the study population

A total of 96 patients were included and the details of the population's baseline characteristics are present in Table 1. Exactly half of the patients were female (48 patients), with a mean age of 65 ± 11 years. Regular alcohol consumption was present in 26 patients (27.1%), and 21 patients reported previous or present smoking (21.9%). One quarter of the patients had family history of GC (24 patients). *H. pylori* infection was identified at Index EGD in 36 patients (37.5%) and all these patients had a successful eradication, despite 15 of them (41.7%) needing 2 or more antibiotic schemes. Concerning the histological diagnosis, most patients had LGD (87.4%), and the location of the dysplasia in random biopsies was most frequently the antrum (67.7%).

Table 1. Baseline characteristics of the study population ($n=96$).

Variable	Study population's characteristics ($n=96$)
Sex – n (%)	
• Female	• 48 (50.0)
• Male	• 48 (50.0)
Age, in years – mean \pm SD	65 \pm 11
Arterial hypertension – n (%)	44 (45.8)
Diabetes mellitus – n (%)	17 (17.7)
Regular alcohol consumption – n (%)	26 (27.1)
Smoker (previous or present) – n (%)	21 (21.9)
Regular NSAIDs use – n (%)	9 (9.4)
Medicated with PPI – n (%)	57 (59.4)
Family history of GC (within three generations) – n (%)	24 (25.0)
Family history of GC (first-degree relatives) – n (%)	11 (11.5)
<i>Helicobacter pylori</i> infection at index EGD – n (%)	36 (37.7)
Presence and location of IM – n (%)	
• Corpus	0 (0.0)
• Antrum	60 (62.5)
• Both	36 (37.5)
Histologic diagnosis – n (%)	
• IFD	10 (10.4)
• LGD	84 (87.4)
• HGD	2 (2.1)
Location of dysplasia in the random biopsies – n (%)	
• Corpus	8 (8.3)
• Antrum	65 (67.7)
• Both	23 (24.0)

Abbreviations: SD – standard deviation; NSAIDs – nonsteroidal anti-inflammatory drugs; PPI – proton-pump inhibitors; GC – gastric cancer; EGD – esophagogastroduodenoscopy; IM – intestinal metaplasia; IFD – indefinite for dysplasia; LGD – low grade dysplasia; HGD – high grade dysplasia.

Table 2. Outcomes of the study population.

Primary endpoint	Patients' outcomes
Endoscopically visible lesion on HD EGD-0 – n (%)	5 (5.2)
Endoscopically visible lesion on HD EGD-FU – n (%)	10 (10.4)
In patients with identified gastric lesion during follow-up – $n=15$ (15.6%):	
Location of the lesion – n (%)	
Corpus	3 (20.0)
Antrum	12 (80.0)
Paris classification of the lesion – n (%)	
0-Is	1 (6.7)
0-IIa	9 (60.0)
0-IIa+b	3 (20.0)
0-IIa+c	2 (13.3)
Size of the lesion, in mm – mean \pm SD	16 \pm 8
Treatment – n (%)	
ESD	10 (66.7)
EMR	3 (20.0)
Surgery	2 (13.3)
Final histologic results of the resected lesions – n (%)	
LGD	7 (46.7)
HGD	7 (46.7)
Adenocarcinoma	1 (6.7)

Abbreviations: HD EGD-0 – High-definition esophagogastroduodenoscopy (initial); HD EGD-FU – High-definition esophagogastroduodenoscopy (follow-up); SD – standard deviation; ESD – endoscopic submucosal dissection; EMR – endoscopic mucosal removal; LGD – low grade dysplasia; HGD – high grade dysplasia.

On gastric evaluation with CE using NBI, areas with a pattern consistent with IM were identified in all patients. A total of 60 patients had IM only in the antrum (62.5%) and 36 patients had IM both in the corpus and antrum (37.5%). The patients' outcomes are detailed in Table 2. An endoscopically visible lesion was identified on HD EGD-0 in 5 patients (5.2%)

Table 3. Factors associated with the presence of an endoscopically visible lesion on HD EGD-FU ($n=91$).

Variables	Presence of lesion ($n=10$)	Absence of lesion ($n=81$)	p
Female sex – n (%)	6 (60.0)	40 (49.4)	0.739
Age – years	69	64	0.245
Regular alcohol consumption – n (%)	5 (50.0)	16 (19.8)	0.047
Smoker (previous or present) – n (%)	1 (10.0)	19 (23.5)	0.450
Regular NSAIDs use – n (%)	2 (20.0)	7 (8.6)	0.257
Medicated with PPI – n (%)	8 (80.0)	46 (56.8)	0.192
Family history of GC – n (%)	3 (30.0)	19 (23.5)	0.699
<i>Helicobacter pylori</i> infection at index EGD – n (%)	8 (80.0)	27 (33.3)	0.012

Abbreviations: HD EGD-FU – High-definition esophagogastroduodenoscopy (follow-up); NSAIDs – nonsteroidal anti-inflammatory drugs; PPI – proton-pump inhibitors; GC – gastric cancer. The statistically significant p values are highlighted in bold.

and on HD EGD-FU in 10 patients (10.4%). In these patients, 80% of the identified lesions were in the antrum and 60% of the identified lesions had a 0-IIa Paris classification. Most patients underwent gastric endoscopic submucosal dissection (ESD) for lesion resection (66.7%). Lastly, the final histologic results of the resected lesions were HGD in 7 patients (46.7%), LGD in 7 patients (46.7%) and adenocarcinoma in 1 patient (6.7%).

Factors associated with the presence of lesion during follow-up

The identification of a lesion on HD EGD-0 was not associated with sex or age ($p=1.000$ and $p=0.804$, respectively), and neither with comorbidities, such as arterial hypertension or diabetes mellitus ($p=1.000$ and $p=0.582$, respectively). Furthermore, the presence of lesion on HD EGD-0 was not associated with *H. pylori* infection at Index EGD, family history of GC or being medicated with PPI ($p=0.647$, $p=0.596$ and $p=1.000$, respectively).

On the other hand, the presence of an endoscopically visible lesion on HD EGD-FU was associated with *H. pylori* infection at Index EGD and with alcohol consumption. Patients with *H. pylori* infection were 8 times more likely to have an endoscopically visible lesion on HD EGD-FU ($p=0.012$) and patients with a regular alcohol consumption were 4 times more likely to have an endoscopically visible lesion on HD EGD-FU ($p=0.047$). The identification of a lesion on HD EGD-FU was not associated with the patient's age ($p=0.245$), sex ($p=0.739$), family history of GC ($p=0.699$) or smoking habits ($p=0.450$). Ongoing medication, namely regular NSAIDs use or chronically medicated with PPI, was not associated with the presence of an endoscopically visible lesion on HD EGD-FU ($p=0.257$ and $p=0.192$, respectively). Factors associated with the presence of an endoscopically visible lesion on follow-up are detailed in Table 3.

The grade of dysplasia detected during random gastric biopsies (HGD versus LGD) was not associated with the presence of a lesion on HD EGD-0 ($p=0.069$), as well as

Table 4. Binary logistic regression for predicting the presence of lesion on HD EGD-FU.

Variable	Odds Ratio	95% confidence interval odds ratio	<i>p</i>
<i>Helicobacter pylori</i> infection at Index EGD	9.3	1.7–50.0	0.009
Regular alcohol consumption	5.0	1.1–22.2	0.033

Abbreviations: HD EGD-FU – High-definition esophagogastroduodenoscopy (follow-up).

comparing IFD *versus* LGD ($p=0.055$) or IFD *versus* HGD ($p=0.455$). The location of the biopsies with dysplasia, corpus *versus* antrum, were not associated with the presence of lesion on HD EGD-0 ($p=0.450$). Furthermore, the grade of dysplasia, HGD *versus* LGD, was also not associated with the presence of a lesion on HD EGD-FU ($p=1.000$), as well as the location of the biopsies with dysplasia, only the antrum *versus* both in the antrum and corpus was not associated with the presence of lesion on HD EGD-FU ($p=1.000$). Additionally, the presence of IM only in the antrum *versus* both in the antrum and corpus was not associated with the presence of lesion on HD-index EGD ($p=0.647$) or on HD EGD-FU ($p=0.100$).

Creating a binary logistic regression, *H. pylori* infection and regular alcohol consumption were identified as statistically significant predictors of the presence of gastric lesion on HD EGD-FU of patients with previous histologic diagnosis of gastric dysplasia in random biopsies (OR 9.3, $p=0.009$ and OR 5.0, $p=0.033$, respectively). The details of the binary logistic regression are present in Table 4.

Discussion

Gastric dysplasia is a neoplastic precancerous lesion [2], with the risk of malignant progression increasing with the histological grade of the dysplasia [6, 14]. Therefore, the histologic diagnosis of gastric dysplasia in random gastric biopsies should prompt further investigation with immediate high quality endoscopic reassessment with CE, followed by endoscopic surveillance within 6–12 months, depending on the grade of the dysplasia [2, 15]. The identification of gastric dysplasia in random biopsies has been associated with an increased risk of GC, up to 6% per year in HGD [14]. In our series, the presence of an endoscopically visible lesion occurred in 15.6% of patients with the previous histologic diagnosis of gastric dysplasia in random biopsies.

The presence of an endoscopically visible lesion on HD EGD-0 occurred in 5.2% of patients, and the fact that a previously not identified lesion was noticed so soon after the Index EGD could be attributable to the superiority of NBI compared to HD-WLE in detecting precancerous lesions. Several studies have shown that CE with NBI has a high concordance with gastric histology, being superior to white-light endoscopy (WLE) and HD-WLE in detecting IM, gastric dysplasia and EGC [16–20]. Furthermore, a prospective study in patients with a histologic diagnosis of HGD or EGC in random biopsies proposed immediate endoscopic reassessment with CE, which had an adequate identification of an

endoscopically visible lesion [21]. Kyoto global consensus has stated that conventional endoscopy is inadequate in diagnosing atrophy and intestinal metaplasia, unlike image-enhanced endoscopy, including CE, which has a high accuracy and reproducibility in the endoscopic diagnosis of precancerous lesions [15]. Pimentel-Nunes et al. showed that NBI had better results than HD-WLE with a sensitivity of 87% for IM and 92% for dysplasia [16]. Gastric endoscopic patterns with CE and magnifying endoscopy with NBI (ME-NBI) have been proven to be reproducible and can effectively diagnose EGC [19, 22].

The presence of an endoscopically visible lesion on HD EGD-FU occurred in 10.4% of patients. In our cohort, most lesions were detected only in the HD EGD-FU. This suggests either the increase in size of a lesion that was not identified on HD EGD-0, or the development of a dysplastic lesion during follow-up in patients with confirmed IM by NBI evaluation. A recent study showed that 8.6% of patients with EGC had a synchronous lesion that was not identified in the initial EGD [23]. A systematic review and meta-analysis revealed that missing GC is not uncommon and younger age (less than 55 years), female sex, marked gastric atrophy, gastric adenoma or ulcer, and inadequate number of biopsy fragments were reported as predictive factors for diagnostic failure [24]. However, the progression rate from IM to dysplasia is not well established [25]. A retrospective study conducted in high-risk Asian immigrants, with an 18-month follow-up period, demonstrated that 14% of patients had IM progression to dysplasia and 2% to adenocarcinoma [26]. Another retrospective study showed that the median time for gastric intestinal metaplasia to progress to adenocarcinoma was 6.1 years, for HGD 3.1 years and for LGD 2.6 years [27]. However, in a low gastric cancer incidence area, for instance Netherlands and Norway, there was a low rate of progression to dysplasia, around 2% [28].

Helicobacter pylori infection at Index EGD was a significant risk factor for having an endoscopically visible lesion on HD EGD-FU, in our series. Since *H. pylori* has been proven to have an important role as a carcinogen, its eradication is the preferred strategy for the prevention of gastric cancer [1, 5, 15, 29]. In fact, persistent *H. pylori* colonisation virtually always leads to chronic gastritis [15]. However, *H. pylori* gastritis can be cured with eradication and its complications avoided [15]. In patients in which *H. pylori* gastritis has progressed to atrophic gastritis, independently of the presence of IM, there is a higher risk of GC and a strategic follow-up endoscopy is required, alongside eradication [15, 30]. European guidelines recommend endoscopic surveillance every 3 years in patients with severe atrophic changes and IM in both corpus and antrum, family history of gastric cancer, incomplete-type IM, or persistent *H. pylori*-associated gastritis [2, 31].

All patients included in our study had IM confirmed on gastric evaluation with CE using NBI, and *H. pylori* eradication was done in all patients with infection, with confirmation of eradication. There was a considerable percentage of patients with an endoscopically visible lesion detected in the follow-up, however, after the histologic diagnosis of gastric dysplasia in random biopsies. This is consistent with the previous knowledge that, even after *H. pylori*

eradication, patients with IM have an increased risk for progression of IM to dysplasia. These patients with atrophic gastritis and IM are still at risk of gastric cancer and need endoscopic surveillance [2, 10, 29]. Nevertheless, *H. pylori* eradication has been proven to reduce the risk of metachronous gastric cancer in cases of previous resected EGC [32–34]. Some recent data seem to challenge the notion that IM is a point of no return [9, 35, 36], with several studies showing that IM reversal can happen gradually over several years after eradication [25, 37–39]. More than half of patients with IM could have histologic regression to chronic gastritis [25, 26]. Aumpan et al. revealed that older age (> 65 years), uncontrolled diabetes mellitus, and persistent *H. pylori* infection were significantly associated with persistent IM or progression to dysplasia [25].

A consumption of 25 or more grams of alcohol per day, every day, was also a risk factor for the presence of endoscopically visible lesion on HD EGD-FU, in our work. Alcohol use has been proven to be an independent risk factor associated with IM progression [40]. However, previous studies had only implicated heavy alcohol consumption, considered as more than 60g of alcohol per day, with the development of GC, even though the same harm did not occur for moderate and light alcohol consumption, less than 60g/day [41, 42]. A healthy lifestyle including not smoking, limited alcohol consumption, healthy diet and normal weight has been associated with a decreased risk of GC [43, 44]. In fact, studies performed in Chinese [45] and Japanese populations [46] identified alcohol consumption as an increased risk factor for dysplasia and adenocarcinoma.

In our study, family history of GC was regarded as the patient's family members having GC within three generations; only a few patients had a first-degree relative with GC. Family history was not associated with the development of a lesion during follow-up in our cohort. This could be attributed to the short follow-up time, which failed to demonstrate the long-term impact of genetic risk factors in GC. Previous evidence suggests that patients with family history of GC, with at least one first-degree relative with a history of GC diagnosed at any age, are at increased risk of progression of CAG until the development of GC [47, 48]. Although with a smaller effect, the presence of second-degree relative with history of GC also increases the risk for GC [2, 49]. However, this can vary between geographic regions and different ethnic groups [47], and the presence of *Helicobacter pylori* infection might contribute to the increased risk of GC [50].

Finally, history of smoking, previous or present, was not associated with the presence of endoscopically visible lesion on HD EGD-FU. Previous studies have identified current and former smoking as risk factors for gastric cancer [51], with highest risk in those with heavy smoking habits, even for previous smokers [52]. The risk decreases with the duration after stopping cigarette smoking [53].

To the best of our knowledge, this is the first study to describe the follow-up of patients with the histologic diagnosis of gastric dysplasia in random gastric biopsies, reporting the incidence of gastric lesion harbouring dysplasia. This study has some limitations, including its retrospective nature, the small sample size and the endoscopic and histological

interobserver variability of the biopsies performed in Index EGD, at the outpatient clinic.

In our sample, 15% of patients with the histologic diagnosis of gastric dysplasia in random biopsies had an endoscopically visible lesion during follow-up and most lesions were identified in the HD EGD-FU. Thus, this study emphasizes the benefits of establishing a learning program in endoscopy training for CE with NBI, as a routine clinical practice in endoscopic surveillance of extensive atrophy and intestinal metaplasia, and to identify suspicious areas for biopsy. Furthermore, our results highlight the importance of adherence to recommended follow-up in these patients with particular attention to patients with *H. pylori* infection at Index EGD and those with regular alcohol consumption of at least 25g of alcohol per day. More studies with a longer follow-up period are important to monitor these patients and identify other risk factors for the occurrence of dysplastic lesions.

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