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ORIGINAL RESEARCH

Endoscopic follow-up in patients with first-degree relatives for gastric cancer: a real-world observational study

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ABSTRACT

Background: First-degree family history of gastric cancer is a risk factor for gastric cancer and precancerous conditions, but only a few studies exist regarding the endoscopic follow-up of these patients. This study investigates endoscopic and histological findings over a 15-year period in patients with first-degree relatives of gastric cancer intestinal type who underwent follow-up upper gastrointestinal endoscopies.

Research design and methods: We conducted a retrospective real-world observational study involving patients who underwent at least two upper gastrointestinal endoscopies between 2008 and 2023 at Sant'Andrea Hospital, Rome. The study analyzed histological findings, dividing participants into four subgroups based on their baseline conditions [H. pylori infection, gastric atrophy, intestinal metaplasia, dysplasia].

Results: One hundred and six patients were included, only 13% were indicated for follow-up endoscopy according to the MAPS guidelines. An additional 13% of patients developed precancerous conditions, most of whom were H. pylori positive at the index examination, with an odds ratio risk of 6.778 ($p = 0.004$).

Conclusions: Performing routinely virtual chromoendoscopy during the index endoscopy in these patients could improve the detection of precancerous conditions. Special attention should be given to H. pylori-positive patients due to their increased risk of developing precancerous conditions, for whom follow-up endoscopies may be beneficial.

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Endoscopy; first-degree relatives; family history; gastric cancer; gastric precancerous conditions

1. Introduction

Gastric cancer [GC] is the fifth most common malignancy and the fourth leading cause of cancer-related mortality worldwide [1]. In Western countries, the primary healthcare challenge associated with GC is its low prevalence, associated with high mortality, as it is often diagnosed at advanced stages. For this reason, a key prevention strategy in these regions is the identification of individuals at increased risk of developing GC. One of the major risk factors is a first-degree relative's history of GC, which is associated with a 2.92-fold increased risk of GC compared to the general population [2]. Moreover, excluding hereditary syndromes and the diffuse histological subtype, the carcinogenesis of intestinal-type GC follows the well-established Correa cascade, which involves the progression from precancerous gastric conditions such as gastric atrophy [GA] and intestinal metaplasia [IM] [3]. In countries with a low to intermediate incidence of GC, the British Society of Gastroenterology guidelines recommend considering endoscopic screening in individuals aged 50 years or older who have multiple risk factors for GC [males, smokers, pernicious anemia], particularly those with a first-degree relative affected by GC, to facilitate the early diagnosis of precancerous conditions and lesions, including GA, IM, and dysplasia [4]. When precancerous conditions are detected, patients should undergo follow-up endoscopic surveillance at intervals recommended by the MAPS II guidelines [Management of epithelial precancerous conditions and lesions in the stomach] [5]. Conversely, no indications for upper GI endoscopy [UGI] surveillance are recommended in the absence of histological or endoscopic abnormalities.

Based on these concepts, we conducted an observational study on the evaluation of endoscopic and histological findings in patients who underwent follow-up UGI endoscopy at our center due to a first-degree family history of intestinal-type GC with a 15-year observation period.

2. Materials and methods

2.1. Study populations

In this retrospective observational study, patients who underwent UGI endoscopy with biopsies according to the updated Sydney system protocol, with the indication for first-degree relatives with intestinal type GC between January 2008 and July 2023 at the Endoscopy department of Sant'Andrea Hospital, Sapienza University of Rome, were included. Then, we considered only patients with an index and a follow-up UGI endoscopy for first-degree relatives with GC for the analysis.

Exclusion criteria were patients under the age of 18, patients with previous gastric surgery, patients who did not undergo biopsies for any reason, inadequate gastric biopsies, second-

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degree family history of GC, relatives of patients with diffuse-type gastric cancer, inherited genetic syndromes [i.e. Hereditary Diffuse Gastric Cancer or Lynch syndrome], and patients who underwent follow-up gastroscopies within less than 1 year.

Written informed consent was provided by all participants, and approval was obtained from the Sapienza Ethical Committee (12SA/2022). The dataset used for this retrospective study was derived from the electronic medical records of the (La Sapienza University of Rome, Sant' Andrea Hospital), which owns and manages these data. Authorization for data use was granted by the hospital's data custodian.

2.2. Endoscopic procedures, biopsies, and histopathological assessment

UGI endoscopies were conducted with the use of pharyngeal anesthesia [*xylocaine* spray puffs] and/or conscious or deep sedation [*midazolam or propofol*]. Biopsies were performed following the updated Sydney system protocol [6], which includes two biopsies from the antrum, one from the incisura angularis, and two from the corpus. Histopathological analysis was carried out by an expert pathologist specializing in upper gastrointestinal pathology [EP]. The histopathological report adhered to the criteria of the updated Sydney system as well as the Operative Link for Gastritis Assessment [OLGA] and the Operative Link on Gastric Intestinal Metaplasia [OLGIM] [7,8]. Gastric mucosal atrophy was defined as a reduction or loss of the original gastric glands, potentially replaced by pseudopyloric metaplasia or IM [9]. The classification of gastric neoplastic lesions followed the Padova International Classification [10] and WHO guidelines [11], which included low-grade intraepithelial neoplasia, high-grade intraepithelial neoplasia, and invasive gastric adenocarcinoma. *H. pylori* infection was diagnosed using modified Giemsa staining.

2.3. Study design

We conducted a retrospective study using the electronic database of the Endoscopy Department of Sant'Andrea University Hospital, focusing on UGI endoscopies performed for the family history of GC from 2008 to July 2023. We included patients with at least two UGI endoscopies performed for a first-degree family history of GC, analyzing both endoscopic and histological findings. Based on the following histological findings observed during the index UGI endoscopy [*H. pylori* infection, precancerous conditions, gastric dysplasia/GC], the included population was divided into four subgroups:

- Group A patients negative for precancerous conditions and *H. pylori* infection
- Group B patients negative for precancerous conditions and positive for *H. pylori* infection
- Group C patients positive for precancerous conditions and for *H. pylori* infection
- Group D patients positive for precancerous conditions and negative for *H. pylori* infection

For each subgroup, histological findings from follow-up UGI endoscopies were analyzed.

2.4. Statistical analysis

Data were expressed as median [range] and/or number/total [%]. Frequency distributions were described for each group. Descriptive statistical analyses were performed using Microsoft Excel [version 2021] and Jamovi [version 2.4.7]. A chi-square [χ^2] test was used to assess whether there was a significant association between groups [A vs. B and C vs. D] and the presence of precancerous conditions at follow-up. If statistical significance was reached, a logistic regression model was applied to estimate the odds ratio [OR] and quantify the strength of the association. No further inferential statistical analyses were performed due to the lack of additional clinically relevant data.

3. Results

The search through the electronic database included 309 patients who underwent UGI endoscopy with an indication of familiarity with GC. Among these, 203 patients were excluded: 13 due to a second-degree family history of GC, 3 due to carrying the CDH1 mutation, 10 patients for incomplete UGI endoscopies, and 177 were excluded because they did not undergo follow-up UGI endoscopy. Finally, 106 patients [70% female, median age 55 (range 27–77)] with a first-degree family history of GC and at least two UGI endoscopies with complete biopsies performed at our center were included (Figure 1). At index UGI endoscopy, no lesions suspicious for GC were detected; however, four patients presented with polyps, one had an elevated area, and five had gastric erosions. Baseline characteristics and endoscopic and histological findings at index UGI endoscopy were analyzed and described in Table 1. Histologically, no cancerous lesions were detected, and in 14 patients [13%], precancerous conditions were identified. According to MAPS II guidelines for gastric precancerous conditions detected at the index UGI endoscopy, only 14 patients [13%] might have required an endoscopic follow-up program: 2 patients for extensive IM, 2 patients for IM restricted to the corpus, and 10 patients for IM restricted to the antrum. The distribution of histological findings was as follows: 60.3% were negative for *H. pylori* and precancerous conditions [group A], 24% were positive for *H. pylori* and negative for precancerous conditions [group B], 6.6% were positive for *H. pylori* and had precancerous conditions [group C], and 9.4% were negative for *H. pylori* but positive for precancerous conditions/lesions [group D]. The baseline characteristics of each group are described in Table 2. Histological findings of the first follow-up UGI endoscopy from each group are shown in Figure 2. The median interval between the index UGI endoscopy and the last follow-up UGI endoscopy was 7 years [range: 1–15 years]. Among 106 patients included, 18 performed three UGI endoscopies and 5 underwent four UGI endoscopies during the observation period.

3.1. Group A: patients negative for precancerous conditions and H. pylori infection

Overall, 64 patients, representing 60% of the study population, were included in group A. Follow-up UGI endoscopies

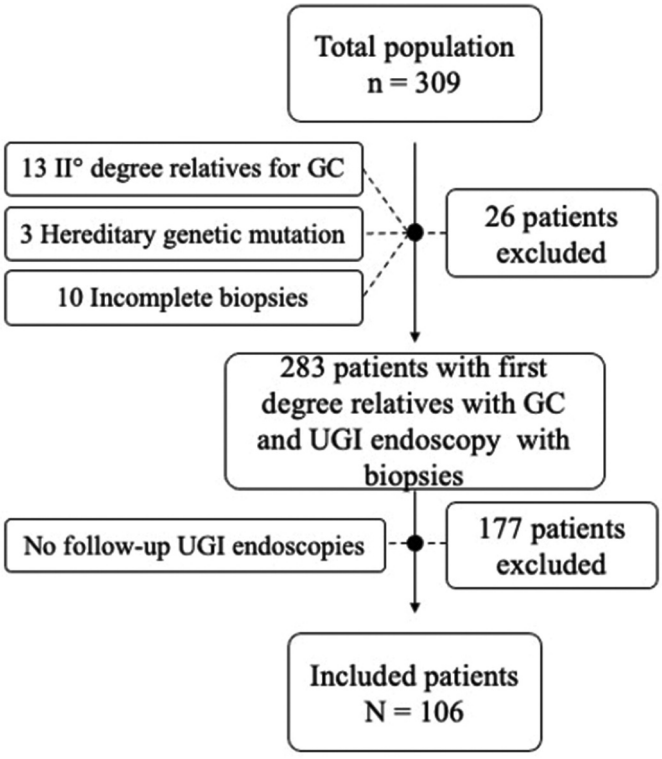

Figure 1. Patient selection flowchart.
Abbreviations: GC: Gastric Cancer; UGI: Upper Gastro-Intestinal.

Table 1. Included patients' characteristics.

Baseline characteristics	n [%]
Overall	106
Female gender	74 [70%]
Median age	55 [27–77]
Affected first-degree relative:	
Unknown	46 [43%]
Father	34 [32%]
Mother	19 [18%]
Sister/Brother	10 [9%]
>1 first-degree family member	4 [4%]
Indications for UGI endoscopy:	
Only family history	54 [51%]
Symptoms	39 [37%]
Anemia	4 [3.7%]
Dysplasia	1 [0.9%]
H. pylori eradication	6 [5.6%]
Others	2 [2%]
Macroscopic findings:	
Elevated areas	1 [0,9%]
Polyps	4 [3%]
Erosions	5 [4,7%]
Cancerous lesions	0
Histological findings:	
Gastric cancer	0
Low-grade dysplasia	2 [2%]
Hyperplastic polyp	1 [0.9%]
Cystic polyp	1 [0.9%]
H. pylori infection	32 [30%]
Extensive atrophic/metaplastic gastritis	2 [2%]
Atrophic/metaplasticcorpus-restricted gastritis	2 [2%]
Atrophic/metaplastic antrum-restricted gastritis	10 [9,4%]
OLGA 0	92 [86,8%]
OLGA 1–2	13 [12,2%]
OLGA 3–4	1 [0,9%]
OLGIM 0	92 [86,8%]
OLGIM 1–2	13 [12,2%]
OLGIM 3–4	1 [0,9%]

were negative for both *H. pylori* infection and precancerous lesions in 59 patients [92%], 1 patient [1.5%] was positive for *H. pylori* infection, while 4 patients [6.5%] developed precancerous conditions, absent at the index UGI endoscopy, but remained negative for *H. pylori* infection. Specifically, two patients developed GA of the corpus/fundus, and two developed antral GA. Among these, three patients had OLGA stage I, and one had OLGA stage II. None of these patients presented IM.

3.2. Group B: patients negative for precancerous conditions and positive for H. pylori infection

In total, 25 patients, representing 24% of the study population, were included in group B. At the first follow-up UGI endoscopy, 16 patients [64%] were negative for *H. pylori* and had no diagnosis of precancerous conditions, while 6 patients [24%] had eradicated *H. pylori* infection but were not diagnosed with gastric precancerous conditions. In three patients [12%], *H. pylori* infection persisted with the development of precancerous conditions in the antrum: two patients with mild GA [OLGA stage I] and one patient with mild IM [OLGIM stage I]. Among these patients, two were *H. pylori*-negative at the second follow-up UGI endoscopy, with no further evidence of precancerous conditions, while the last patient exhibited persistent mild antral GA and IM [OLGA/OLGIM stage I] at the third follow-up UGI endoscopy.

3.3. Group C: patients positive for precancerous conditions and H. pylori infection

In group C, seven patients representing 6.6% of the study population were included. At the first follow-up, six patients [86%] were negative for *H. pylori*, including two patients who were also negative for precancerous conditions [29%] with OLGA/OLGIM stage 0 and four patients with persistent precancerous conditions [57%] with three with OLGA/OLGIM stage I restricted to the antrum and one patient with OLGA/OLGIM stage II with extensive precancerous conditions. One patient [14%] had persistent *H. pylori* infection, but no precancerous conditions were detected in the follow-up UGI endoscopy [OLGA/OLGIM stage 0].

3.4. Group D: patients positive for precancerous conditions and negative for H. pylori infection

Altogether, 10 patients, representing 9.4% of the study population, were included in group D.

At the index UGI endoscopy in this group, two polyp lesions with precancerous lesions, including low-grade dysplasia, were found. Both lesions were endoscopically removed. For these two cases, follow-up endoscopies were performed with a median follow-up of 36 months [range: 12–48 months], with OLGA and OLGIM stage 0 and negative *H. pylori* at follow-up UGI endoscopies, and no metachronous lesions were observed. For the other patients, two showed the regression of precancerous conditions, OLGA/OLGIM stage 0, while in six patients, precancerous conditions persisted. Specifically, one patient had extensive mild GA and IM with OLGA/OLGIM stage I. Another patient had

Table 2. Groups' characteristics based on endoscopic and histological findings at the index UGI endoscopy.

Group n [%]	Female n [%]	Median age [range]	Mean follow-up time in years [range]	*H. pylori* infection	Precancerous conditions
A – 64 [60]	48 [75]	53 [34–76]	6.9 [1–15]	–	–
B – 25 [24]	15 [60]	55 [27–69]	7.3 [1–15]	+	–
C – 7 [6.6]	6 [86]	58 [48–67]	5.3 [1–14]	+	+
D – 10 [9.4]	5 [50]	67 [54–77]	7 [1–13]	–	+

metaplastic atrophic gastritis of the corpus/fundus and was subsequently diagnosed with a Gastric Neuroendocrine Tumor G1, which was endoscopically resected. The remaining four patients had mild-to-moderate metaplastic atrophic gastritis of the antrum [two patients with OLGA/OLGIM stage I and two with OLGA/OLGIM stage II].

3.5. Subgroup comparison

The comparison between groups A and B for the presence of precancerous conditions in UGI endoscopies follow-up showed a statistically significant difference ($\chi^2 = 9.83$, $p = 0.002$). Group B showed a higher prevalence of precancerous conditions (9/25; 36%) compared to Group A (4/64; 6.2%). Logistic regression analysis indicated that the estimated risk of precancerous conditions was 6.15% in Group A and 30.77% in Group B, with an OR of 6.778 (95% CI: 1.914–27.902, $p = 0.004$), as shown in Figure 3. Conversely, no significant difference was observed between groups C and D ($\chi^2 = 0.135$, $p = 0.714$).

4. Discussion

This observational real-world study showed that particular attention should be given to patients with *H. pylori* infection at the index UGI endoscopy for first-degree relatives with GC, as they could develop precancerous conditions during the follow-up. However, following MAPS guidelines, these patients would not have required follow-up, highlighting the lack of recommendations and evidence on the follow-up management of patients with first-degree relatives with GC. Only two recent Swedish epidemiological studies investigated a population of patients with a first-degree relative affected by GC and demonstrated a higher risk of developing GC among those whose relatives had precancerous changes compared to individuals without a family history of gastric disease [12]. Regarding the affected relatives, the study indicated a higher risk among siblings, consistent with previous studies [13]. One of the two studies specifically analyzed a selected population of male patients, reporting a hazard ratio of 1.56 [95% CI 1.15–2.12] for GC risk [14]. Additionally, a recent cross-sectional study suggested that the risk of precancerous conditions and GC appears higher in patients with a male relative affected by GC [15]. In our study, we specifically focused on the detection of precancerous conditions and *H. pylori* infection, analyzing a region with a low incidence of GC. Our study showed that, according to MAPS guidelines, only 13% of patients would have required follow-up UGI endoscopies. However, in our cohort, 13% of patients, who following MAPS guidelines would not have required endoscopic follow-up, developed precancerous conditions during the follow-up UGI endoscopies. Among these, at the index UGI endoscopy, four patients were negative for *H. pylori* and precancerous conditions, while eight patients were positive for *H. pylori* infection. There are no established recommendations for endoscopic follow-up in patients without precancerous conditions and *H. pylori* infection (group A), representing most of our cohort [60%]. Among these patients, histologically relevant findings remained absent in 92% at follow-up, while 8% developed new histological abnormalities that were not present in the index endoscopy. This percentage could potentially be reduced by performing high-quality endoscopic examinations according to guideline-recommended protocols [16] and implementing routine virtual chromoendoscopy, which permits targeted biopsies [17]. For patients with *H. pylori* infection, eradication therapy is recommended regardless of the presence or absence of precancerous conditions, followed by endoscopic confirmation of eradication [18]. While the majority of patients successfully eradicated the infection, particular attention should be given to those in whom *H. pylori* persists, as they have multiple risk factors for GC [19]. Regarding post-eradication precancerous conditions, these remain present in most patients, as also demonstrated by previous studies indicating that *H. pylori* eradication is associated with regression only of gastric atrophy but not with regression of IM, even in its early stages [20]. Moreover, among patients who were positive for *H. pylori* infection but negative for precancerous conditions at the index UGI endoscopy (Group B), 32% developed precancerous conditions at follow-up UGI endoscopies. This highlights a high-risk subgroup in which an indication for follow-up UGI endoscopy could be beneficial. Our study has several strengths. The topic is underexplored, and our long observation period includes 15 years. Another key strength is the high quality of endoscopic and histological assessments conducted by expert endoscopists and pathologists, who utilize standardized histological classification systems for precancerous and cancerous gastric conditions. We consider this aspect fundamental for the interpretation of our results and their clinical applicability. Additionally, the study has a low exclusion rate due to incomplete biopsy sampling. In fact, patients with a first-degree family history of GC who undergo UGI endoscopy without biopsy sampling are inadequately managed, as they will likely require repeat endoscopy in the future.

However, our study also has some limitations. Its retrospective design may have introduced selection bias, leading to a reduced sample size. Moreover, incomplete endoscopic reports and missing clinical or laboratory data limited our ability to perform further statistical analyses and more detailed stratifications, including exploration of potential risk factors suggested by previous literature, such as familial clustering, age at onset of the index case, EBV status, and co-occurrence of other malignancies. Finally, this is a real-world observational study rather than an interventional one, and as such, it is limited to describing and characterizing the phenomenon under investigation, while providing directions for future research. For this reason, prospective

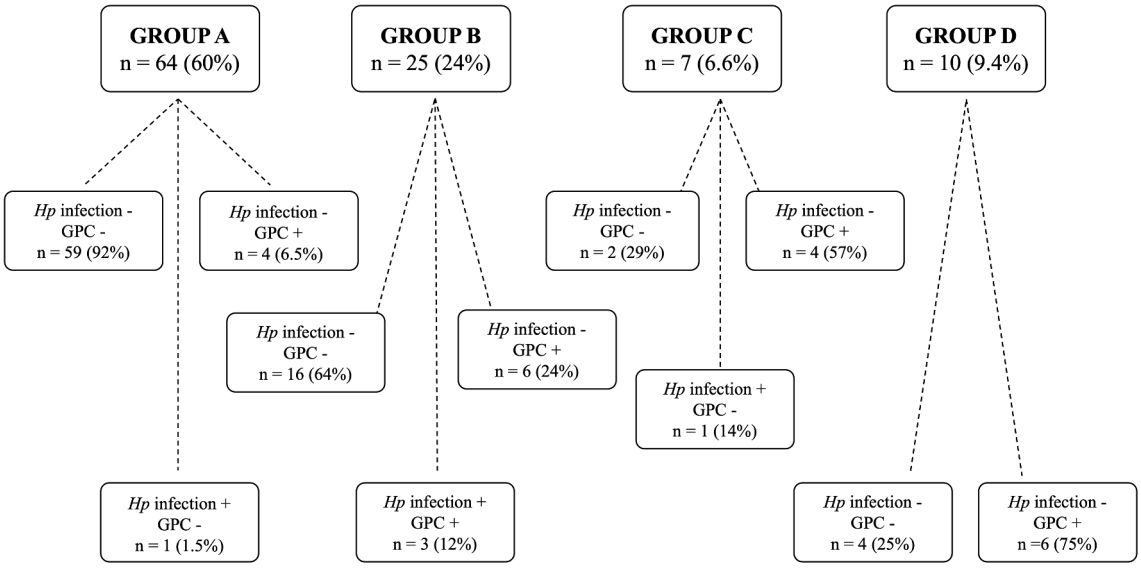

Figure 2. Histological findings of the subgroups at the follow-up UGI endoscopies.
Abbreviations: GPC gastric precancerous conditions.

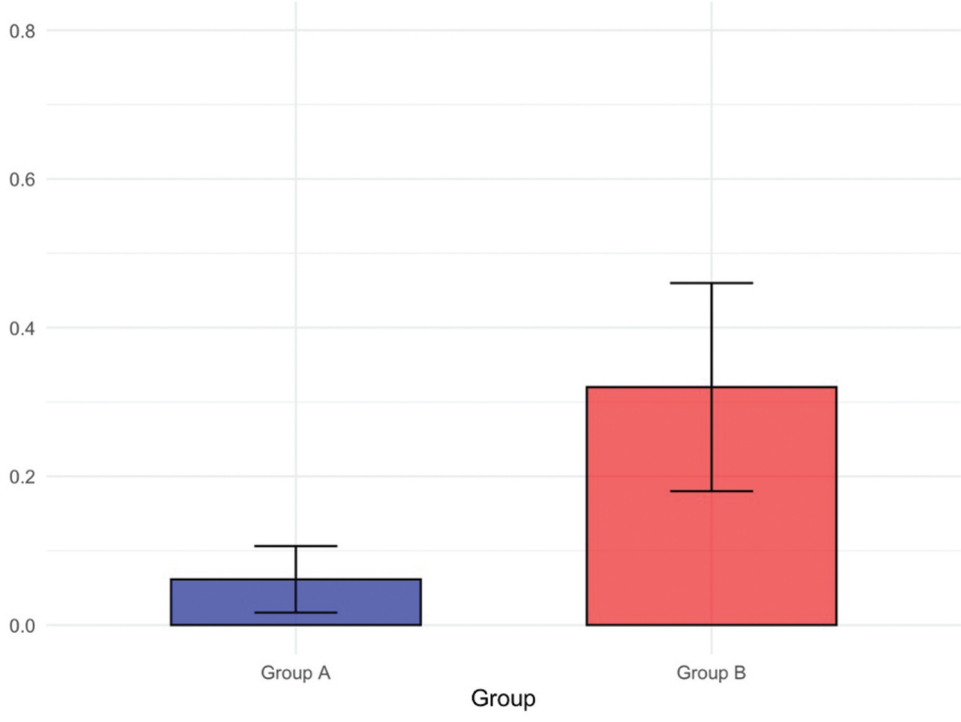

Figure 3. The estimated probability of precancerous conditions by group.

protocols are necessary to better assess the medical burden associated with patients who have a first-degree relative affected by GC. Finally, it is important to note that our study does not include hereditary GC syndromes with distinct and well-defined management recommendations [21], and it specifically focuses on the intestinal-type pathway of gastric carcinogenesis. Diffuse-type GC was not included, as specified in the Methods, because it follows a different pathogenic mechanism and is guided by separate, well-established diagnostic and surveillance recommendations [22].

5. Conclusions

In conclusion, focusing on the intestinal-type pathway of gastric carcinogenesis, this study highlighted that, in addition to patients with precancerous conditions who require endoscopic follow-up according to MAPS guidelines, approximately one-third of patients who were *H. pylori* positive but initially negative for gastric precancerous conditions developed such conditions during follow-up, suggesting that increased attention should be given to this group. Regarding patients who are negative for precancerous conditions and *H. pylori*

infection at the index UGI endoscopy, our results confirm that these patients do not require follow-up endoscopic examinations, but we recommend the implementation of routine virtual chromoendoscopy to improve the identification of precancerous conditions at the index UGI endoscopy. This methodological approach would help in defining the patient's risk of precancerous and cancerous gastric conditions, reducing unnecessary endoscopic examinations, and the risk of misdiagnosis.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Author contributions statement

Irene Ligato, Emanuele Dilaghi, Giulio Cozza, Emanuela Pilozzi, Edith Lahner, Francesco Panzuto, Annibale Bruno, and Gianluca Esposito contributed substantially to the conception and design of the work. Data acquisition, analysis, and interpretation were performed by Irene Ligato, Emanuele Dilaghi, Giulio Cozza, Emanuela Pilozzi, Edith Lahner, Francesco Panzuto, Annibale Bruno, and Gianluca Esposito. All authors were involved in drafting the manuscript or critically revising it for important intellectual content. All authors gave final approval of the version to be published and agree to be accountable for all aspects of the work, with responsibility for addressing any questions regarding the accuracy or integrity of any part of the work, including the authorship list.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, G Esposito upon reasonable request.

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