ARTÍCULO DE REVISIÓN

Gastric remnant cancer: a comprehensive narrative review from carcinogenesis to treatment

Cáncer de remanente gástrico: una revisión narrativa integral desde la carcinogénesis hasta el tratamiento

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ABSTRACT
Gastric remnant cancer is cancer secondary to partial gastrectomy after five years. Peculiarities due to the gastrectomy status may influence this type of GC. Modifications in the gastric microbiome, luminal pH, dietary habits, increased bile reflux, and Epstein-Barr virus infection, together with the traditional GC risk factors, cooperate to increase the risk of cancer in the remnant stomach. *H. pylori* infection has been widely associated with GC, and its role in the pathogenesis of the remnant stomach, as well as the preventive effect of its eradication after gastrectomy, are issues of great scientific interest. Bariatric surgery is another condition potentially related to increased GC risk and challenges to its diagnosis. In this scenario, this article aims to review the current evidence of the fundamental aspects involved in developing the gastric remnant cancer
Keywords: *Metachronous gastric cancer; remnant gastric cancer; gastric stump; H. pylori infection; precancerous lesions (source: MeSH NLM).*

RESUMEN
El cáncer en el remanente gástrico (CRG) es secundario a una gastrectomía parcial después de cinco años. Las peculiaridades del estado de la gastrectomía pueden influir en este tipo de GC. Las modificaciones en el microbioma gástrico, el pH luminal, los hábitos dietéticos, el aumento del reflujo biliar y la infección por el virus de Epstein-Barr, junto con los factores de riesgo tradicionales de CG, cooperan para aumentar el riesgo de cáncer en el estómago remanente. La infección por *H. pylori* se ha asociado con discreción en la patogénesis del CRG; por lo tanto, su efecto preventivo de erradicación después de la gastrectomía, son temas de gran interés científico. La cirugía bariátrica es otra condición potencialmente relacionada con el aumento del riesgo de CRG y los desafíos para su diagnóstico. En este escenario, este artículo tiene como objetivo revisar la evidencia actual de los aspectos fundamentales involucrados en el desarrollo del CRG.
Palabras clave: *Cáncer gástrico metacrónico; cáncer gástrico remanente; muñón gástrico; infección por H. pylori; lesiones precancerosas (fuente: DeCS Bireme).*

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Introduction

Gastric cancer (GC) is a permanent problem around the world. However, incidence and mortality have had a slow decline during the last decade in many countries, and this cancer still represents a significant challenge in public health worldwide. According to the Global Observatory of Cancer (GLOBOCAN), in 2021, there were an estimated one million new cases per year and 770,000 deaths, being the fourth leading cause of cancer death globally [1-3]. Gastric remnant cancer (GRC) is defined as carcinoma that appears after gastrectomy [4]. Some authors describe a GC detected more than five years following surgery, while others suggest using a 10-year interval. It is controversial to establish GRC; it has been suggested that the diagnosis of GRC may be due to a preexisting carcinoma that was not detected endoscopically before gastrectomy or is a residual carcinoma of the primary tumor [5]. The Chinese research and guidelines defined GRC as a new cancer occurring in the residual stomach more than 5 or 10 years after gastrectomy [6]. The incidence is discordant, has been estimated between 2-6% of all GC types [4,7-9], whether secondary to benign or malignant pathology; however, with a different biological behavior depending on the etiology [9]. In a recent study, the incidence rate of GRC after proximal gastrectomy was 8.9% [10]. For the other part, GRC comprises between 1-8% of all gastric neoplasms [11-14]. Besides, the detection in advanced stages contributes to low rates of curative resection and poor outcomes [9,15]. In this landscape, endoscopic screening enhanced diagnosis at an early stage [14,16-18].

The development of primary GC occurs through a stereotypical pathological pathway, which Pelayo Correa proposed [19]. This cascade defines that over several decades, and due to *H. pylori* infection, some individuals present alterations of the gastric mucosa through histopathological phases that precede the development of GC [19]. Likewise, other aspects are fundamental in carcinogenesis, such as decreased gastric acid secretion, leading to a higher intraluminal pH, decreased somatostatin secretion, and consequent gastrin secretion. In addition to stimulating gastric acid secretion by parietal cells, gastrin also improves proliferation in the area of gastric epithelial stem cells, which leads to an increase in epithelial cell turnover [20]. The GC precancerous cascade is a multi-phase process in which environmental, genetic, and epigenetic factors interact [21]. Under these circumstances, given that precancerous lesions have been described in GRC, they may also be involved; however, their role in the progression of GRC still needs to be elucidated.

On the other hand, according to Kim and colleagues study, *H. pylori* eradication on the ocurrence of GRC has a not preventive effect [22]. In this context, this article aims to review the current evidence of these fundamental aspects of GRC, such as precancerous lesions and progression to cancer, diagnosis, and *H. pylori* eradication.

Definition

GRC is defined as carcinoma that appears after gastrectomy. GRC has been classified into the following categories: a) cancer of unknown origin developed in the gastric remnant; b) cancer that remains in the gastric remnant after initial gastric surgery; c) metachronous gastric cancer; and d) recurrent cancer in the gastric remnant [23]. These are considered the mechanisms of carcinogenesis in GRC after distal gastrectomy differ between the initial cause of the surgery, whether benign disease or gastric primary cancer (GPC) [24]. Primer disease has shown that the risk of GRC is high in normal mucosa [25-28].

The metachronous gastric cancer (MGC), consisting of gastric cancers detected within one year after endoscopic resection, should be regarded as a missed synchronous GC [29]. An overview of MGC as a GC located distant from the original GC over one-year following esophagogastroduodenoscopy (EGD) [29].

Risk factors and etiopathogenesis

The risk factors associated with GRC are mainly those that could be considered in GC carcinogenesis. In this context, the determinant factors of health, such as age, male sex, heavy alcohol intake, high salt consumption, smoking, low potable water, red meat, and a diet deficient in fruits, vegetables, and low antioxidants have been described [7,24,30-33]. For its part, Epstein-Barr virus (EBV) has been involved with gastric carcinogenesis. EBV is a human herpes-γ virus 4 with a double-stranded DNA virus [34], which causes various human cancers, including Burkitt´s lymphoma, Hodgkin lymphoma, nasopharyngeal carcinoma, and GC [35]. Although the precise mechanism by which EBV-infected gastric epithelial cells is unknown, the hypothesis that sustains it lacks the CD21 receptor and direct cell-cell interaction between EBV-infected B lymphocytes and gastric epithelial cells [36,37]. In GPC, the meta-analysis studies reported that approximately 8.7% of GC had EBV in tumor cells [38]. However, in RGC, the EBV prevalence rate was four times higher, with 35.1% for postsurgical GRC [38]. Moreover, they do not receive adequate care for ineffective and fragmented health systems, inadequate services, disparities, and barriers to access to esophagogastroduodenoscopy (EGD), lack of knowledge, and high financial costs [31,39,40]. Is remarkable the role played by the *H. pylori* infection have shown in the mucosa of the remnant [4,7,41,42]. On the other hand, gastrectomy for primary GC causes changes in the gastric microenvironment (GME) that induce chronic injury to the normal mucosa of the remnant, triggering a carcinogenic pathway that, in the long term, develops into GRC [25,43-45]. Additionally, the vagotomy, which consists of denervation of the gastric mucosa and leads to hypochlorhydria [24,26,41,46], and it contributes substantially to the carcinogenesis of the remnant [4]. Other independent factors associated with GRC are male sex, atrophy of the gastric mucosa and multiple tumor lesions [41,46,47]. The patients with precancerous changes in the mucosa of the remnant show an increased risk of developing GRC. In this sense, Shiotani *et al.* [48],

demonstrated that atrophy in the lesser curvature of the gastric corpus was associated with an increased risk of cancer. In addition, elevated serum pepsinogen I level (25 ng/mL), aberrant DNA methylation, microsatellite instability (MSI), aberrant expression of miRNAs, expression of CD44v by tumor cells, and intramucosal neoplasia are also considered risk factors microscopic of RGC [49].

Some authors have investigated GRC in distal gastrectomy for benign pathology to elucidate the progression GRC. In this regard, two significant factors have been reported to be responsible for the change in the environment affecting the remnant mucosa after gastrectomy and chronic damage attributed to enterogastric reflux and denervation of the gastric mucosa [25-28,50]. The study conducted by Miwa *et al.* [51], has demonstrated that enterogastric reflux has potent carcinogenic activities. In the murine model, it was observed that denervation of the gastric mucosa to promotes carcinogenesis in the gastric remnant [26]. In another study, they demonstrated clinicopathological divergences in the way GRC develops after benign disease and GRC secondary to GPC [9]. In this respect, murine models with the oral carcinogen N-methyl-N´-nitro-N-nitrosoguanidine (MNNG), with Billroth-II (B-II) showed increased adenocarcinoma in the gastric remnant in comparison to control animals without MNNG, and it's related with the severity of the enterogastric reflux [25]. GRC must be recognized for gastrectomy after benign disease for that stump carcinoma is localized in the anastomosis; this site is severe enterogastric reflux [25]. In addition, bile acids such as deoxycholic acid (DCA) are recognized as cocarcinogens in colorectal cancer because they induce DNA damage and apoptosis in human colon epithelial cells [52]. Furthermore, bile acids such as deoxycholic acid (DCA) are recognized as cocarcinogens in colorectal cancer because they induce DNA damage and apoptosis in human colon epithelial cells [52]. Bile acids are also believed to play a key role in GC because nitrosative derivates of taurocholic and glycocholic bile acids induce tumors in murine models [53]. Interestingly, several other factors considered injurious to the gastric mucosa, such as bile acids, can also contribute to induced CDX gene expression in gastrectomy patients, leading to GIM development. These factors may also promote progression to neoplasia [54].

The procedure type has been considered as a critical risk factor. In this respect, it has been observed that the risk of GRC recurrence was more common at the connection site in the B-II reconstruction. This difference is likely because the connection site is regularly exposed to enterogastric reflux after B-II reconstruction, leading to ongoing mucosal inflammation, regeneration, and cell transformation. Sustained cell proliferation due to chronic inflammation at the connection site after distal gastrectomy may lead to precancerous conditions such as atrophic gastritis and intestinal metaplasia [55]. In another study in which partial gastrectomy secondary to peptic ulcer disease was evaluated, B-II reconstruction was considered to have a higher risk of developing to GRC than B-I reconstruction since it demonstrated a significant correlation with GRC compared to B-I reconstruction after distal gastrectomy [56]. These studies showed that the occurrence of GRC ranged

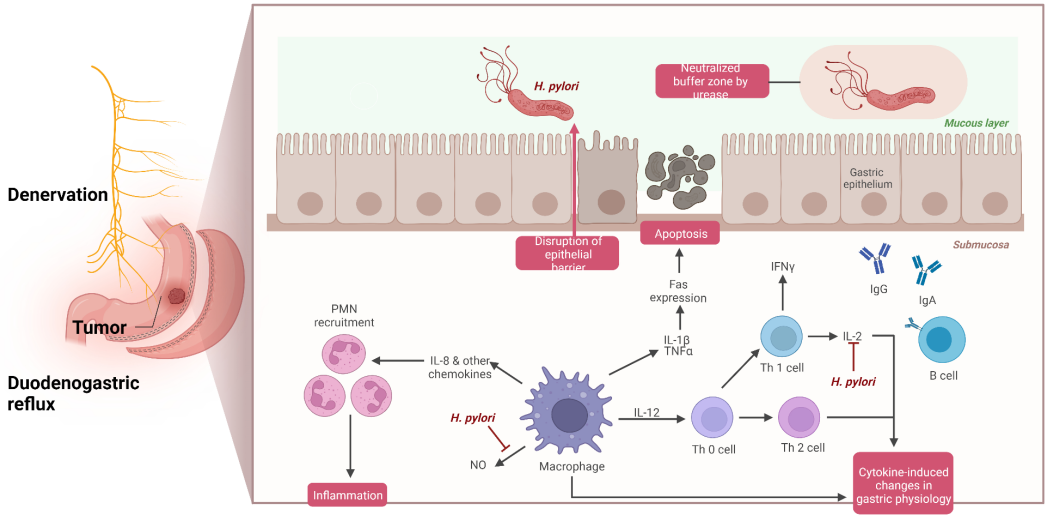

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Figure 1. Possible mechanisms of carcinogenesis in GRC and its role by *H. pylori* infection.
H. pylori trigger the chronic inflammatory response, and in its cascade, it is a crucial IL-8, a proinflammatory interleukin role in PMN recruitment released by macrophages. Furthermore, this cell releases other interleukins, such as IL-12, responsible for Th0 polarization, and Th1 releases IFN-γ and Th2, cytokine-induced changes in gastric physiology. The IL-1β and TNF-α also released by macrophages and induced apoptosis and endothelial cell injury. Besides, denervation and duodenogastric reflux contributed to GRC carcinogenesis. Created with www.bioRender.com

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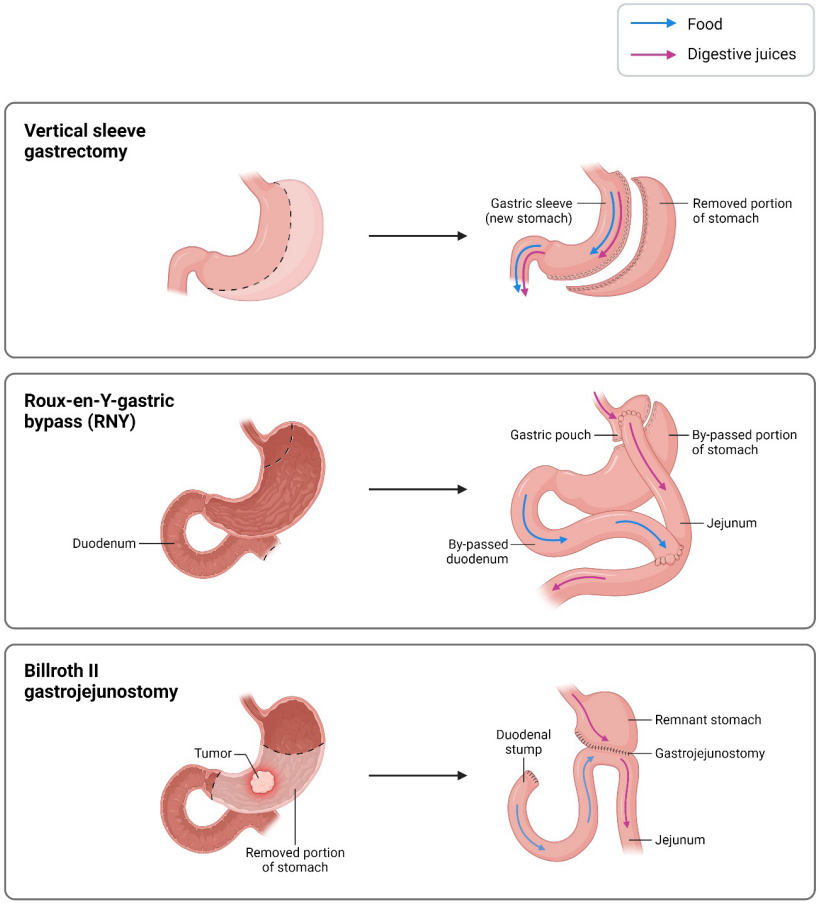

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Figure 2. Surgery types in GC.

from 0.9% to 12.9% [42]. A random effects model was adopted to pool results since significant heterogeneity indicated among these studies (p 1⁄4 0.000, I2 1⁄4 91.0%) [42]. GRC is more likely to appear in the B-I reconstruction and B-II reconstruction. Therefore, Roux-Y reconstruction should be chosen preferentially since this reconstruction has superiority in preventing reflux symptoms to reduce the risk of carcinogenesis at the GRC [57,58]. Moreover, *H. pylori*-induced gastritis has a synergic effect with bile reflux in stimulating cellular proliferation in the GRC [59-61]. Therefore, the risk of GRC occurrence may be also related to *H. pylori* infection; however, needs to be further studied [42].

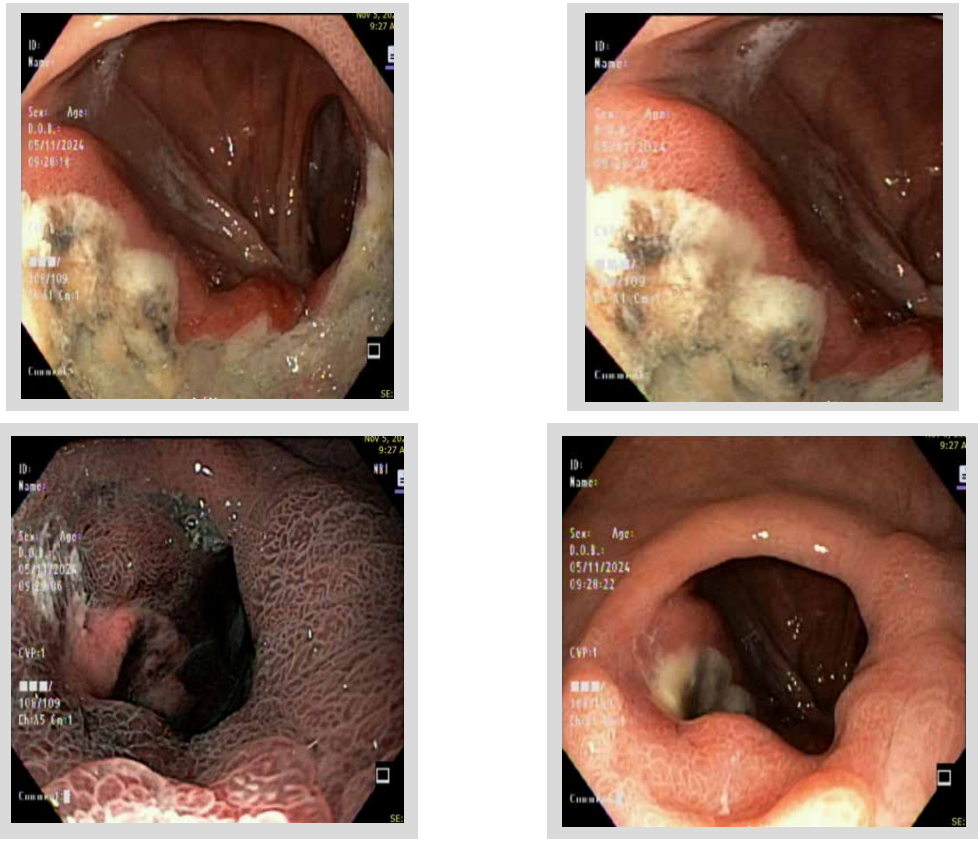
The *oncocarriers* of variant genes and the addition of *H. pylori* infection have shown an predisposition to risk of GC [62]. The germline pathogenic genes (APC, ATM, BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, and PALB2) were associated with the risk of GC. Consistent with this idea, they can play a role in GRC, and further research is necessary in this context.

H. pylori infection is perhaps the most crucial risk factor contributing to the progression of GRC. In the concept extrapolated from primary infection for GC, it has been consistently accepted since its presence triggers proliferative and antiapoptotic cascades, being considered a carcinogenic driver [31,63], and its eradication can reduce the prevalence of this type of cancer [64]. *H. pylori* is a Gram-negative bacteria equipped with a series of mechanisms to ensure its survival in a hostile niche, characterized by a low partial pressure of oxygen and high concentrations of gastric acid and digestive enzymes [65]. The residual post-gastrectomy mucosa is considered hostile to *H. pylori*; hence H. *pylori* infection progressively decreases following surgery. This is due to at least three reasons: a) the antrum, which is the *H. pylori* natural environment, has been removed; b) the increased pH due to biliopancreatic reflux inhibits *H. pylori* proliferation [50,66-68]; and lastly, c) the residual mucosa is replaced by an infection-resistant atrophic-metaplastic epithelium [50]. *H. pylori* has a spiral shape that allows it to attach and survive to the environment through adaptation mechanisms that include the ability to

Source: Images provide by co-author Megan Neumann from Pontificia Universidad Catolica de Chile.

Figure 3. Descriptions of diagnostic and endoscopic imaging in GRC. **A**) Computerized tomography of abdomen and pelvis with contrast in frontal sectional. **B**) Axial sectional. In both sections, parietal thickening of the gastric remnant with a probable infiltrative appearance is observed (marked by a white arrow).

harness the microaerophilic environment, the expression of the enzymes such as urease and mucinase that modulate the environment by forming an ammonium cloud of more carbon dioxide, which leads to an increase in pH and the flagella that provide mobility, allowing access to deep layers of the mucosa of the stomach wall, beyond using the host's defenses to develop a survival niche and the hook protein and the adhesins (OipA, BabA, SabA) that allow it to adhere to gastric epithelial cells [69,70]. Multiple virulence factors are known as CagA, VacA, CagL, and iceA [27]. Virulence factors associated with the cytotoxin-associated pathogenicity island (CagPAI) gene have probably been studied most emphatically. The notable virulence factor is CagA, an oncoprotein translocated in the host into epithelial cells by a type IV secretion system [27,72,73]. This mechanism is mediated by the specific interaction of CagL with the αVβ6 integrin, promoting the secretion of CagA within gastric epithelial cells [72,74]. CagA virulence factor crosstalk with numerous intracellular effectors, resulting in a pro-inflammatory and mitogenic response, disruption of cell-cell junctions, loss of cell polarity, and transformation of gastric epithelial cells [27,75,76]. CagA virulence factor can promote GC tumorigenesis through multiple cell signaling pathways, such as WNT/β-catenin, PI3K/AKT, Sonic hedgehog (SHH), JAK/STAT3, NF-κB, Janus kinase, and ERK/MAPK signaling pathways [75-77]. In addition, CagA induces the production of the enzyme spermine oxidase, which causes injury and oxidative stress in gastric epithelial cells. This facilitates the conditions of a subpopulation of cells resistant to apoptosis and, consequently, with a high potential for malignant transformation [44,77,78]. In one study, subjects were infected with *H. pylori* containing the CagA gene associated with more severe gastric pathology and gastric adenocarcinoma than subjects infected with CagA-negative strains [79]. It has been estimated that CagPAI is present in approximately 60-70% of Western *H. pylori* strains and 100% in East Asian *H. pylori* strains [79,80]. In Colombia, a country with a high incidence of GC, it has



Source: Images provide by co-author Megan Neumann from Pontificia Universidad Catolica de Chile.

Figure 4. Direct endoscopic images may show infiltrative lesions at the level of the anastomotic remnant.

been estimated that *H. pylori* infects more than 70-80% of the adult population, and the strains obtained from symptomatic patients are positive-CagA [81-84].

H. pylori infects the gastric mucosa in more than half the population around the world [85]. At a global level, the prevalence is wildly divergent; the reports vary widely. In particular, the differences are due to multiple factors, such as geographic location, age, ethnicity, and socioeconomic conditions [86]. *H. pylori* infection in the GRC has been reported from 17.4% to 68.2% [87]. Likewise, the prevalence of *H. pylori* infection varied over time following surgery, being 29.5% less than 25 years after gastric resection, 13.6% from 16 to 30 years after surgery, and 10% > 30 years later [50]. Indeed, overall *H. pylori* infection occurs in 50-68.2% of distal-gastrectomy patients, in 55-72% of B-I patients, in 58–66% of B-II, and in 26% of patients reconstructed by Roux-Y surgery [50]. Other studies have confirmed *H. pylori* infection rates in patients treated by B-II reconstruction lower than those observed in subjects treated by B-I or Roux-Y reconstruction [88,89]. In a study conducted by Chan *et al*. [90] showed that Roux-Y reconstruction causes less reflux during fasting and in the postprandial period, and a lower incidence of *H. pylori* infection than B-II reconstruction, even when B-II is associated with Braun's anastomosis [50]. Moreover, in the meta-analysis conducted by Mak *et al*. shown that the pooled prevalence of GRC was 2.6% (95% confidence interval (CI), 2.2-3.0%, p=0.000) [42]. On the other hand, some authors have reported that *H. pylori* infection driver the **Correa's cascade** and transforms normal epithelial tissue into chronic atrophic gastritis and intestinal metaplasia, which are considered precursor conditions of malignancy for GC [21,31,63,78]. In GRC, chronic active inflammation of the mucosa is associated with *H. pylori* as a triggering mechanism [31,44,91]. Therefore, *H. pylori* eradication in the GRC has been shown to improve the degree of chronic active gastritis [92]. *H. pylori* eradication has likely been linked to preventing GRC following distal gastrectomy. In this sense, it has been proposed that young patients with moderate atrophic gastritis and in the absence of enterogastric reflux are the best candidates for *H. pylori* eradication therapy since they retain a high probability of *H. pylori* colonization in the gastric remnant [93].

Effects of *H. pylori* infection on gastric atrophy and Intestinal metaplasia after gastrectomy

A possible cause of residual gastritis is due to *H. pylori* infection synergist by biliary enterogastric reflux [94]. It has been formulated to be beneficial for eradicating *H. pylori* in patients after gastrectomy and for gastric atrophy and

intestinal metaplasia in the remnant. Given the scenario, Fukuhara *et al.* [95], tested interleukin-8 (IL-8) concentrations as a sensitive marker of inflammation in the gastric mucosa three months after surgery. The authors determined that in the absence of *H. pylori* infection, the concentrations of IL-8 were 13, 56, and 87 pg/mg in groups A (Roux in Y) and Billroth (B-I and B-II), respectively ($p<0.05$). On the other hand, in the cases of *H. pylori* infection, IL-8 concentrations were 61, 161, and 234 pg/mg in the different study groups ($p<0.01$), which allow to authors of this study, suggest that there is a more severe inflammatory response in the presence of *H. pylori* infection. Moreover, both bile reflux and *H. pylori* infection have been implicated as independent risk factors for developing gastritis and intestinal metaplasia in the gastric remnant after distal gastrectomy. Therefore, the study conducted by Cho *et al.* [96], found that the *H. pylori* eradication can lead to regression of gastric atrophy and intestinal metaplasia in the remnant at 36 months after subtotal gastrectomy. On the other hand, Abe *et al.* [66], examined the severity of gastritis in the remnant of 184 patients undergoing distal gastrectomy with B-I (106 cases) and B-II (36 cases), as well as jejunal interposition (42 cases). *H. pylori* infection was confirmed in 55.6% of patients with B-I and 76.1% with jejunal anastomosis ($p<0.05$) [66].

Findings in the gastric remnant after gastrectomy

The need for gastrectomy in patients with peptic ulcer has decreased since the discovery of *H. pylori* and the use of proton pump inhibitors. The sequelae of gastrectomy are recurrent ulcers, especially marginal ulcers or GRC. The incidence of marginal ulcers has been reported to range from 0.6% to 16% [97]. *H. pylori* infection is the leading risk factor for gastric ulcers; however, its role in marginal ulcers after surgery is not clarified. In the study carried out by Chung *et al.* [98], which included 78 patients with endoscopic ulcers and 759 patients without ulcers after gastrectomy, indicating that the incidence of ulcers after gastrectomy was 9.3% and 92% corresponded to marginal ulcers, more frequent in patients with B-I anastomosis [98]. According to study conducted by Leivonen *et al.* [59], from 155 patients only 41 patients were determined to have an ulcer at the anastomosis site with a recurrence rate of 34% after B-II reconstruction, about 14% in Roux-Y, and about 24% in B-I reconstruction [59]. Ischemic ulcers related to the surgical technique must be considered among the leading etiologic causes for these types of ulcers [99].

The change of the gastric microenvironment after gastrectomy

Food retention and bile reflux are frequently observed in patients undergoing subtotal gastrectomy for primary GC [100]. Additionally, the gastric juice's biochemical and microbiological profile and pH are altered. In this sense, in a previous study, the presence of N-nitrosamine components and bacteria in gastric juice after gastric surgery was evaluated, demonstrating that those patients who underwent gastric resection B-I and B-II had a higher pH, increased N-nitrosamine concentrations, positive nitrate reductase bacterial counts, and anaerobic bacterial counts [101]. The gastric remnant will reduce ascorbic acid concentrations in a higher pH microenvironment. This antioxidant scavenges carcinogenic N-nitrosamines, reactive oxygen species (ROS), and reactive nitrogen species (RNS). Oxygen and nitrogen free radicals induced by inflammation may increase the risk of developing to GC. Likewise, variations in gastric juice's microbiological and biochemical microenvironment may also play a crucial role [102].

After gastrectomy, residual mucosa in the stomach is considered a risk factor for developing GRC. Chronic inflammation due to enterogastric biliary reflux produces hyperplastic changes in the remnant. In the study conducted by Becchi *et al.* [103], found that hyperplastic changes gradually decreased with increasing distance from the anastomosis, meaning that gastric histological findings after partial gastrectomy were affected by reflux. For his part, Fukuhara *et al.* [104] evaluated the association between bile reflux and gastritis in 62 patients undergoing curative gastrectomy for GC. The results showed that the correlation was independent for *H. pylori* infection, and the researchers concluded that biliary enterogastric reflux after distal gastrectomy may cause residual gastritis [104].

Diagnosis and follow-up

EGD is the best method for diagnosing GC; however, it can be a challenge in GRC. This does not form exophytic masses but instead follows a pattern of submucosal infiltration [31,78,105]. Therefore, the diagnosis becomes significantly difficult when linitis plastica (LP) occurs [106].

EGD with biopsy taking has been considered the ideal diagnostic tool for diagnosing precancerous lesions. The follow-up interval has not been very well established. Choe *et al.* [107] concluded that a period of exhaustive observation for the early detection of GRC on an annual basis had a more significant impact on the follow-up of chronic atrophic gastritis [107]. It should also be noted that severe atrophic gastritis is an independent risk factor for GRC (OR: 3.8, 95%; IC: 1.4-10.1, $p=0.0008$) [107].

To follow-up and confirm *H. pylori* eradication in low and middle-income countries (LMIC), diagnostic tools with a sensitivity of more than 80%, such as urea breath test (UBT) or rapid urease test (RUT) are good options for non-resected patients [108]. Nevertheless, reduced stomach size and bile reflux decrease the chances of *H. pylori* identification after gastrectomy. Additionally, because UBT passes through the residual stomach more quickly, it is not recommended in patients undergoing gastrectomy; and in this sense, the *H. pylori* detection in the remnant is broad range of 19-70% [108,109]. Since the remnant stomach carries a higher risk for GC, endoscopies with multiple biopsies should be recommended.

H. pylori eradication

Currently, *H. pylori* eradication is recommended in patients with gastroduodenal diseases such as peptic ulcer disease,

mucosa-associated lymphoid tissue lymphoma (MALT), and GC [31,105,110,111].

H. pylori infection is considered a crucial factor for predisposing the development of cancer after partial gastrectomy. The emerging evidence is discussed. In this respect, Fukase *et al*. [64], in a randomized, open-label clinical trial, confirmed that *H. pylori* eradication after endoscopic resection of early GC was beneficial after three years of follow-up. In contrast, in the study conducted by Maehata *et al*. [46], in patients with GRC after endoscopic resection of GPC, the rates of GRC were 14.3% in the persistent *H. pylori* infection group and 8.5% in the non-infection group (p=0.262). The authors suggest that *H pylori* eradication does not reduce the incidence of metachronous gastric cancer and *H pylori* eradication should be performed before the progression of gastric mucosal atrophy. It should be noted study conducted by Choi *et al*. [112], controversial results showed that there were no significant differences in the development of GRC; in this study, the incidence of GRC between the two groups did not differ significantly at 1, 2, 3, and 4 years after *H. pylori* eradication. The long-term effect of *H. pylori* eradication on the development of GRC was determined [112]. Another study, during a mean 5-year follow-up period, GRC developed in 22 patients in the eradication group and 43 in the control group (HR = 0.497; p=0.008). These findings suggest that *H. pylori* eradication prevented the development of GRC during the long-term follow-up period [113] .

A well-designed prospective cohort study revealed that *H. pylori*-positive patients undergoing gastrectomy for GPC had a higher risk of malignant precursor lesions compared with *H. pylori*-negative patients (OR = 4.20, IC 95%: 1.10-15.96) being less significant compared to positive-*H. pylori* patients undergoing gastrectomy for duodenal ulcer (OR = 1.59, 95% CI: 0.44-5.73) [87]. This may be indirect evidence that *H. pylori* eradication therapy prevents the development of GRC after prior gastrectomy [87].

On the other hand, a recent randomized clinical trial in Korea showed that 4 of 190 patients had GRC after gastrectomy during a median follow-up of 5 years [96]. There were no differences in GRC development according to *H. pylori* eradication. However, the limitations of this study were the small number of patients, the short observation period, and the mucosal conditions differed in many aspects related to postoperative bile reflux that destroyed the parietal cells. These results indicate that the incidence of GRC after endoscopic resection does not decrease unless there is early eradication before the progression of gastric atrophy [112]. Long-term follow-up is necessary to determine the long-term effect of *H. pylori* eradication on the development of GRC after endoscopic resection of early-GC. These findings are consistent with those of similar studies [55,114].

For another part, according to an RCT conducted by Choi *et al*. [23], demonstrated that during a follow-up of 6 years, the MGC development in 14 patients (7.2%) in the treatment arm and 27 patients (13.4%) in the placebo arm [HR: 0.50; CI 0.26-0.94; p=0.03]. The insight of this study is an improvement from the baseline of atrophy grade at gastric corpus in 48.4% of the patients (treatment arm) [p<0.001]. Therefore, the authors suggest that eradication treatment for *H. pylori* reduces the risk of GC, and the benefit of *H. pylori* eradication does not eliminate the risk because the premalignant conditions remain. Another point is that a significant reduction in gastric atrophy is observed after six years of post-eradication. Recently, a cohort retrospective study explored the potential benefits of anti-*H-pylori* eradication therapy after radical gastrectomy in patients with GC and positive *H. pylori* infection. In this study, survival analysis showed that five years overall survival rates were 94.1% [95% CI, 89.3%-99.2%; HR: 0.33, p=<0.001] (anti-*H. pylori* arm) and 73.8% [95% CI, 70.7%-77.0%; HR: 0.33, p=<0.001] (non-anti-*H. pylori* arm). The authors concluded that anti-*H. pylori* eradication is associated with improved survival in patients with GC with *H. pylori* infection [115].

The Maastricht VI/Florence Consensus recommends *H. pylori* eradication in patients with previous gastric neoplasia treated with endoscopic or subtotal gastric resection, which appears to expand the indication to include adenoma or dysplasia under the terminology of neoplasia [105], to reduce the risk of GC may be more effective if eradication occurs before the development of preneoplastic conditions [46,116,117]. Under these circumstances, Latin America and the Caribbean Code Against Cancer 1st Edition Cancer Prevention and Experts Recommendations for Cancer Gastric Prevention and Control in The Americas consistently reinforces these evidence-based decisions [39,40].

In this recent systematic review conducted by Temido *et al*. [118], proposed that Hybrid therapy (HT) without bismuth has a similar eradication rate, compliance and adverse effects rates, and better safety profile. The Argentinean Registry on *H. pylori* Management showed that standard triple effectively was between 77.96% and 90% adjusted dose kg/weight [119]. This scenario is crucial since it is peremptory that the follow-up of the *H. pylori* eradication is successful. A Korean nationwide study included 28.091 elderly patients with early GC who underwent endoscopic resection (50.2%) and received *H. pylori* eradication during a median follow-up of 4.3 years, of which 3.186 patients developed a metachronous lesion. Besides, received *H. pylori* eradication reduced metachronous recurrence (adjusted hazard ratio [aHR], 0.89; 95% confidence interval [CI], 0.83-0.96), demonstrated that *H. pylori* eradication was associated with a reduced risk of metachronous recurrence in elderly patients [120]. In a systematic review, Ford *et al*. [121] conclude that exist evidence in favor of the active search and that *H. pylori* eradication reduces the incidence and mortality from GC in asymptomatic individuals; however, the main limitation is that the results come from East Asian populations. The above allows us to suggest that it is urgent to propose research studies with the Latin American population. Some factors must also be considered for the success of *H. pylori* eradication. In this

order of ideas, the optimal time for *H. pylori* eradication in gastrectomy patients is not established; however, the effectiveness of *H. pylori* eradication therapy depends on the gastric pH, the bacterial load, the level of drug in the gastric mucosa and the pattern of acquired and local resistance [31]. In this respect, Liou *et al.* [122] demonstrated that antibiotic resistance, CYP2C19 polymorphisms, and bacterial virulence factors are essential in successful *H. pylori* eradication. The bacteria can produce β-lactamases in the gastric juice of the remnant, leading to the transfer of drug-resistance genes and interference with the effectiveness of eradication [123]. *H. pylori* eradication rate in the GRC was 90% after first-line triple therapy, which was comparable to rates of 85-88% in non-surgical patients [124]. After gastrectomy, alkaline duodenopancreatic juice neutralizes gastric acid, which inhibits the growth of *H. pylori*. In this context, *H. pylori* bacterial load would be considered small in gastrectomy patients, so a brief triple therapy regimen could be effective. Additionally, there was no difference in eradication rates between the 3-day and 7-day treatment groups (90.9% vs. 93.8%) [125].

In bariatric surgery, the gastric sleeve allows the follow-up of precancerous lesions, unlike gastric bypass [45]. In this context, if they have OLGA III-IV, a resective bypass is suggested, since the stomach cannot be explored, if there is GC, it is diagnosed late [126]. Additionally, studies targeting the excluded stomach have shown increased rates of precancerous lesions and DNA damage. Conversely, sleeve gastrectomies increase gastroesophageal reflux, a known risk factor for gastroesophageal junction cancer.

Regarding the determination of non-invasive markers for detecting precursor lesions of malignancy, an attempt has been made to evaluate the levels of IL-1β and its correlation with *H. pylori* eradication in premalignant lesions. In this scenario, it has been observed that IL-1β can serve as a potent inhibitor of gastric juice secretion; besides, Kato *et al.* [127] demonstrated that IL-1β levels lead to gastric dysplasia and correlated it with higher pH in the remnant after *H. pylori* eradication. However, a meta-analysis that evaluated the role of IL-1β and IL-1 receptor antagonist gene polymorphisms on the risk of GRC showed an association in patients of European ancestry but not in Asian ancestry [128].

According to the Maastricht VI/Florence consensus statement, serology is the only test that is not affected by local changes in the stomach, which can avoid false negative results [105]. This is because antibodies against *H. pylori*, its more specific antigen CagA, remain elevated despite transient decreases in bacterial load and for long periods after the disappearance of *H. pylori* from the stomach [129]. *H. pylori* stool antigen test is also a reliable, non-invasive diagnostic tool with a sensitivity of 93% and a specificity of 100% [31,105,125].

Remarks conclusions

It has been suggested that gastric juice's biochemical and microbiological profiles change dramatically after gastric surgery. It is hypothesized that this surgical procedure could increase the occurrence of enterogastric biliary reflux and potentially trigger a chronic inflammatory state of mucosa in the stomach. Bile reflux, gastric denervation, and *H. pylori* infection appear to have a synergistic effect on cell proliferation in the remnant and may explain the increased risk of GC after gastrectomy. *H. pylori* infection is not a sufficient factor in the genesis of cancer after gastrectomy; however, further research is necessary to determine its critical role in this context. Given the scenario, a rigorous prospective study (cohort study) or randomized clinical trial is necessary to evaluate the clinical relevance of *H. pylori* eradication and long-term benefits. Additionally, changes in the gastric microenvironment, EBV infection, and gastric dysbiosis may have a role in GRC.

According to available current evidence, the recommendations of the Maastricht VI/Florence, Asian-Pacific Consensus, and Latin America and Caribbean Code Against Cancer 1st edition agree on the *H. pylori* eradication in patients with previous gastric neoplasia already treated with endoscopic or subtotal gastrectomy consistent to local resistance profiles, first-line quadruple or triple therapy effectively eradicates *H. pylori* in gastrectomized patients.

Serology is the only test not affected by local changes in the stomach; a combination of serology with a histological biopsies or an *H. pylori* stool antigen test can diagnose *H. pylori* infection in remnant gastric and avoid false negative results.

Moreover, EGD with multiple biopsies should be recommended. The follow-up of precancerous conditions in this context of the OLGA/OLGIM III/IV is premptory due to the high-risk of progression to GC.

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