Microb Health Dis 2024; 6: e1043

GASTRIC PRECANCEROUS CONDITIONS OR LESIONS AND *HELICOBACTER PYLORI*

M. Areia[1,2], M. Dinis-Ribeiro[2,3,4]

[1]Gastroenterology Department, Portuguese Oncology Institute of Coimbra (IPO Coimbra), Coimbra, Portugal
[2]RISE@CI-IPO (Health Research Network), Portuguese Oncology Institute of Porto (IPO Porto), Porto, Portugal
[3]Gastroenterology Department, Portuguese Oncology Institute of Porto (IPO Porto), Porto, Portugal
[4]MEDCIDS/Faculty of Medicine, University of Porto, Porto, Portugal

Corresponding Author: Miguel Areia, MD; email: miguel.areia75@gmail.com

Abstract – Gastric cancer is one of the most common malignancies and a leading cause of mortality worldwide, mainly caused by *Helicobacter pylori* (*H. pylori*).

A PubMed literature search was performed to obtain relevant publications associated with gastric precancerous conditions or lesions and *H. pylori*, published between April 2023 and March 2024. Articles that were considered the most pertinent to the topic were selected.

One meta-analysis confirmed that *H. pylori* eradication reverses atrophic gastritis and intestinal metaplasia. One double-blind, randomized, folic acid-controlled trial confirmed that Moluodan, a patented Chinese traditional medicine that suppresses the activation of the Wnt/β-catenin signaling pathway, reverses low-grade dysplasia in *H. pylori*-negative patients.

One multicenter, case-control study confirmed that individuals with advanced stages of atrophy, according to the histologic Operative Link on Gastritis Assessment staging system, are at higher risk of cancer and two review articles provided further evidence regarding the relation between gastric intestinal metaplasia and cancer, further supporting the knowledge that individuals with extensive or incomplete intestinal metaplasia are at higher risk of gastric cancer, including those with spasmolytic polypeptide-expressing metaplasia (SPEM). One cross-sectional study confirmed that individuals with advanced stages of atrophy, according to the endoscopic Kyoto and Kimura-Takemoto classifications, are at higher risk of cancer, while another study further supports the need for an incisura biopsy for gastric cancer risk assessment.

Two studies provided further insights regarding the relation between dynamic tuft cell expansion, gastric precancerous conditions, and dysplasia and between gastric cancer and gastric diffuse large B-cell or mucosa-associated lymphoid tissue lymphomas.

Finally, a new review article about gastric cancer in Western countries updates the data supporting primary prevention by *H. pylori* eradication, but also secondary prevention by endoscopic surveillance of precancerous conditions or endoscopic screening when combined with a colonoscopy performed for colorectal screening.

Keywords: Atrophy, Metaplasia, Gastric cancer, *Helicobacter pylori*.

INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies and a leading cause of mortality worldwide[1]. Intestinal-type GC represents the large majority of GC cases and typically originates from chronic atrophic gastritis, mainly caused by *Helicobacter pylori* (*H. pylori*)[2]. *H. pylori* infection

causes chronic gastritis that, after decades, may transform into atrophic gastritis (AG), which might progress to intestinal metaplasia (IM), dysplasia, and adenocarcinoma (the Correa cascade)[3]. These different stages in gastric carcinogenesis and the risk factors that initiate this process are well-known, treatable, and potentially surveyable, providing an opportunity for both primary and secondary preventive measures, including GC screening[4,5].

METHODS

A PubMed literature search was performed to obtain relevant publications associated with gastric precancerous conditions or lesions and *H. pylori*, published between April 2023 and March 2024. The search terms used included "*helicobacter pylori*", "precancerous", "premalignant", "atrophy" and "intestinal metaplasia". The Boolean operator "AND" was used between "*helicobacter pylori*" and the other terms; "OR" Boolean operator was also used to obtain relevant combinations and generate the search results. Selected articles were those that the authors considered the most pertinent to the review topic.

H. PYLORI ERADICATION REVERSE ATROPHIC GASTRITIS AND INTESTINAL METAPLASIA

Liang et al[6] performed a meta-analysis to estimate the effect of *H. pylori* eradication on atrophic gastritis and intestinal metaplasia.

Authors searched PubMed, Web of Science, and EMBASE databases through April 2023 for studies providing scores of atrophy or IM before and after *H. pylori* eradication. In total, 20 articles were included, comprising 7 randomized controlled trials and 13 cohort studies (including 9 new prospective cohort studies not included in previous publications), comprising 5,242 participants. Studies were from Asia, Europe, and America, 17 of which had more than 3 years of follow-up, and all evaluated AG or IM using the Sydney system. *H. pylori* eradication significantly improved the AG score (OR 2.96; 95% CI: 1.70-5.14, $p<0.01$) and the IM score (OR 2.41; 95% CI: 1.24-4.70, $p<0.01$), both in the antrum and corpus, compared to placebo. Although a high heterogeneity was present, the results remained significant in subgroup analyses by study design, gastric locations, populations, and follow-up time.

The findings provide further evidence for *H. pylori* eradication by significantly improving AG and IM at the early stages, with a large sample size and a sufficiently long follow-up period.

MOLUODAN REVERSES LOW-GRADE DYSPLASIA IN *H. PYLORI* NEGATIVE PATIENTS

Zou et al[7] performed a double-blind, randomized, multicenter (19 Chinese centers) folic acid-controlled trial to investigate the clinical potential and safety of Moluodan to reverse gastric precancerous lesions. Moluodan is a patented Chinese traditional medicine approved by the State Food and Drug Administration in China that suppresses the activation of the Wnt/β-catenin signaling pathway[8].

Patients diagnosed with AG or IM, with or without low-grade dysplasia, and negative for *H. pylori*, were randomized into one of four active treatment groups, for 12 months, in a 2:2:1:1 ratio: Moluodan group (once daily), folic acid group (10 mg, twice per week), combination group (Moluodan one daily and folic acid twice per week), and high-dose Moluodan group (3 times daily). Randomization was computer-based and drug-blinded, and a combination of active and placebo pills allowed a blinded allocation and double-blinded treatment.

The primary outcome was the improvement of global histological diagnosis at one-year follow-up endoscopy, defined as a decrease in at least one stage using the Operative Link for Gastritis Assessment (OLGA), the Operative Link for Gastric Intestinal Metaplasia assessment (OLGIM), and the disappearance rate of dysplasia. This outcome was assessed by an upper endoscopy with histopathology at baseline and at the last follow-up visit.

Between 2017 and 2021, 502 subjects were randomly assigned to Moluodan (n=166), folic acid (n=168), combination (n=84), or high-dose Moluodan group (n=84). By intention to treat analysis, improvement in global histological diagnosis was: Moluodan (39.5%), folic acid (37.8%), combined

drugs (32.1%), and high-dose Moluodan (47.4%), without statistical significance. High-dose Moluodan had an improved protective efficacy *vs.* the common dose, again without statistical significance. The disappearance rate of dysplasia was 82.8% for Moluodan, 53.8% for folic acid, 61.1% for the combination group, and 56.3% for the high-dose Moluodan, reaching statistical significance between Moluodan and folic acid groups ($p<0.01$). The rate of serious adverse events was 4.2%, 10.7%, 7.1%, and 6.0%, respectively, some of them requiring drug discontinuation, mostly due to liver dysfunction, but without significant differences between groups.

In conclusion, Moluodan three times daily for one year, compared to folic acid, was equivalent in improving gastric precancerous conditions but better for reversing low-grade dysplasia. Further randomized controlled trials are needed, including placebo control, other populations, a better definition of endoscopic assessment of outcomes, and safety issues, to further evaluate the effectiveness of Moluodan for gastric cancer prevention.

INDIVIDUALS WITH ADVANCED STAGES OF ATROPHY ARE IDENTIFIED TO BE AT HIGHER RISK OF CANCER

Carlosama et al[9] conducted a multicenter, case-control study to evaluate the association between the histologic Operative Link on Gastritis Assessment (OLGA) staging system and the risk of gastric dysplasia and cancer.

A total of 506 patients were recruited from three Colombian centers. Patients with a histologic diagnosis of gastric dysplasia or cancer were considered cases (n=91), while patients with a histologic diagnosis of AG or IM were regarded as controls (n=415). The endoscopic and histopathologic studies were done using the Sydney system and the OLGA staging.

Patients presented atrophy in 23%, intestinal metaplasia in 59%, dysplasia in 10%, and cancer in 8%. Advanced OLGA III-IV stages were more frequent in cases with dysplasia or cancer *vs.* controls, 55.0% *vs.* 10.7%. In multivariate regression analysis, OLGA III-IV provided a higher risk of dysplasia and gastric cancer (adjusted OR 8.71; 95% CI: 5.09-14.9), as well as age >50 years (adjusted OR 3.14; 95% CI: 1.58-6.23). The overall diagnostic ability of OLGA III-IV for gastric dysplasia or cancer was: a sensitivity of 54.9% (95% CI: 50.6-59.2), specificity of 89.3% (95% CI: 89.2-89.4), and a positive likelihood ratio of 5.17.

This study further supports other published literature that the OLGA staging system is a good marker for the selection of patients at higher risk of gastric dysplasia and cancer.

Individuals with Extensive or Incomplete IM are Identified to be at Higher Risk of Cancer

Sugano et al[10] provided a review article in 2023 regarding the relation between gastric IM and intestinal type gastric cancer. They reviewed the scientific evidence that strongly supports this well-known and significantly associated relation and proposed a new progression model that builds on the Correa cascade.

Gastric IM is a pathologic change of the gastric mucosa that develops as a consequence of a regenerative process and is strongly associated with chronic inflammation and AG. True metaplasia, according to the authors, should be defined as a phenotypic conversion through differentiation reprogramming at the level of stem cells, thereby resulting in clonal changes in the whole gland; as such, “trans-commitment” might be a preferred term for the reprogramming event causing clonal changes of the gland.

Upper gastrointestinal endoscopy is the current standard method for the detection of IM, and the development of image-enhanced endoscopy has allowed improved visual detection of IM and targeted biopsies. Regarding IM and increased gastric cancer, the two most important risk factors are distribution and type. Considering IM distribution, endoscopic mapping biopsy studies have shown that widespread IM represents a high-risk state. The OLGIM tool, with a quantitative assessment of stages by taking biopsy specimens from five sites (greater and lesser curvature of the distal antrum, greater and lesser curvature of the proximal corpus, and incisura angularis), has shown that higher stages of OLGIM were strongly associated with increased cancer incidence[11]. Considering IM type, among complete and incomplete subtypes, incomplete GIM is associated with the highest risk of cancer[12].

The molecular mechanisms leading to IM induction are not fully elucidated, but there is evidence for both direct bacterial action, such as *H. pylori*, and indirect mechanisms through inflammatory cytokine expression like bile acids. *H. pylori* infection is the most important etiologic factor, and a high prevalence of infection is correlated with increased IM and GC risk. *H. pylori* eradication is the most important method for preventing GC, but the effect of eradication on established GIM is still debated.

Therefore, endoscopic surveillance for IM may be necessary, especially for higher OLGIM stages. Recent European, British, and American guidelines recommend surveillance in high-risk groups at 3 to 5-year intervals, and advances in image-enhanced endoscopy with integrated artificial intelligence might impact preventive strategies in the near future[4,13,14].

Individuals with Spasmolytic Polypeptide-Expressing Metaplasia (SPEM) are at Higher Risk of Gastric Cancer and Associated with *H. Pylori* Infection

Li et al[15] published a review about the relationship between spasmolytic polypeptide-expressing metaplasia (SPEM) and GC. The spasmolytic polypeptide-expressing metaplasia (SPEM) is a specific type of mucous cell metaplasia that plays a functional role in the repair of gastric epithelial injury and seems to be more strongly linked to GC than IM.

Data demonstrates that SPEM represents the major reparative lineage responsible for wound healing. However, chronic inflammation and immune responses caused by *H. pylori* can induce further progression of SPEM to IM, dysplasia, and adenocarcinoma. SPEM and IM are two different lineages of metaplastic cells, and the current mainstream view is that the progression of SPEM leads to IM. *H. pylori* infection is a predisposing factor for SPEM but also causes chronic inflammation and immune response, promoting parietal cell loss, SPEM development, and metaplasia expansion[16].

Chong et al[17] provided another review regarding the role of SPEM in gastric carcinogenesis.

The emergence of SPEM is intimately connected to the plasticity of chief cells, indicating that the transformation into SPEM occurs not only in the chief cell zone but also in the basal region. The mature chief cells in the isthmus region function as reserve stem cells in the metaplastic process, capable of reprogramming into various cell types, contributing to the formation of SPEM cells[18].

Chronic *H. pylori* infection causes mural cell loss or oxyntic atrophy and marked inflammation. Mural cells have an essential role in the differentiation of the entire gastric lineage, being involved in the secretion of several signaling factors. With the loss of parietal cells, these signaling molecules are not secreted properly, leading to the reprogramming of the chief cell transcriptome that finally transdifferentiates into SPEM. The marked inflammation throughout the mucosa can induce SPEM gene expression[19]. As the appearance of SPEM has been found to precede IM, the detection of early SPEM provides new opportunities for future diagnosis and treatment.

INDIVIDUALS WITH ADVANCED STAGES OF ENDOSCOPIC CHANGES SUGGESTING ATROPHY ARE IDENTIFIED TO BE AT HIGHER RISK OF CANCER

Nguyen et al[20] performed a cross-sectional, single-center study in Vietnam to address the use of the endoscopic Kyoto and Kimura-Takemoto classifications for the diagnosis of high-risk gastric precancerous lesions and active *H. pylori* infection.

Dyspeptic patients without previous upper gastrointestinal endoscopy or *H. pylori* eradication, who underwent an upper gastrointestinal endoscopy at a tertiary hospital, were scored using both endoscopic classifications. There were 5 experienced gastroenterologists performing the exams, using high-definition scopes and with previous local training in endoscopic scoring. High-risk gastric precancerous conditions or lesions were defined as severe and extensive AG, extensive or incomplete IM, or dysplasia. *H. pylori* infection was determined by rapid urease test and histology. The performance of each endoscopic classification was graded by the area under the receiver operating characteristic curve (AUC).

There were 292 patients included, with 14.0% presenting high-risk gastric precancerous lesions and 61.3% *H. pylori* infection. For the presence of high-risk gastric precancerous lesions, Kyoto *vs.* Kimura-Takemoto classifications had comparable performance, AUC: 0.792 *vs.* 0.791; p=0.96, but for the prediction of *H. pylori* infection, the Kyoto classification performed better than the Kimura-Takemoto classification: AUC: 0.77 *vs.* 0.66; p<0.001.

In conclusion, both Kyoto and Kimura-Takemoto endoscopic classifications had comparable performance in predicting high-risk gastric precancerous lesions, but the Kyoto classification performed better for *H. pylori* infection detection.

NO NEED FOR A BIOPSY IN THE INCISURA FOR RISK ASSESSMENT

Ferrari et al[21] published one more study to evaluate the relevance of performing a biopsy in the incisura angularis for better grading a patient's GC risk.

In this observational, prospective, unicentric Brazilian study, 350 patients without GC underwent an upper gastrointestinal endoscopy with biopsies according to the Updated Sydney system, allowing the gastric cancer risk assessment from the OLGA and OLGIM systems, evaluated with and without the assessment of the incisura angularis biopsy.

The prevalence of precancerous conditions or lesions of the gastric mucosa were: 33.4% for AG, 34% for IM, and 1.1% for dysplasia. When comparing both biopsies protocols, corpus + antrum *vs.* corpus + antrum + incisura angularis, the proportion of patients with higher OLGA and OLGIM stages III-IV did not change significantly, either by the OLGA system (6.9% *vs.* 7.4%; p=0.78) or the OLGIM system (7.7% *vs.* 8.3%; p=0.99).

In conclusion, this is another study that opposes the need for the incisura angularis biopsy to diagnose patients with more advanced stages of AG or IM.

RELATION OF DYNAMIC TUFT CELL EXPANSION AND GASTRIC PRECANCEROUS CONDITIONS AND DYSPLASIA

Jang et al[22] explored the alterations in tuft cells during gastric tumorigenesis from AG to IM, dysplasia, and cancer. In this American study, they studied the correlation between tuft cell populations in humans with relevant mouse models of AG, foveolar hyperplasia, IM, and GC.

Tuft cells are chemosensory cells, epithelial in origin, but similar to immune cells in function, mediating the host response to various microbial infections, and being associated with luminal homeostasis, immune response, and tumorigenesis in the gastrointestinal tract[23]. Authors found increased tuft cell numbers associated with foveolar hyperplasia and parietal cell loss, *H. pylori*-induced inflammation, atrophy, and metaplastic glands, compared to normal gastric mucosa, with a significant positive association with the extent of foveolar hyperplasia, inflammation, and IM, in both the corpus and antrum, with the presence of IM being the strongest factor. Finally, in the later stages of gastric tumorigenesis, while 33% of gastric adenomas exhibited 20 or more tuft cells per core, no tuft cells were observed in 77% of GC.

In conclusion, these results suggest that tuft cells increase in AG, IM, and dysplasia but decrease in GC. This suggests that tuft cell expansion is associated with precancerous conditions, but their ultimate loss is associated with progression to GC.

GASTRIC CANCER AND PRECANCEROUS CONDITIONS IN PATIENTS WITH GASTRIC DIFFUSE LARGE B-CELL (DLBCL) OR MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) LYMPHOMAS

Feng et al[24] explored the relationship between the concomitant presence of precancerous conditions and primary gastric lymphoma. The occurrence of primary gastric lymphoma is closely related to *H. pylori*, especially mucosa-associated lymphoid tissue (MALT) lymphomas and some diffuse large B-cell lymphomas (DLBCL)[25].

In this retrospective study in three Chinese centers, 5.1% of patients with primary gastric lymphoma were diagnosed with GC, metachronous (3.2%), or synchronous (1.9%), with a 3-year median diagnosis interval between both cancers, most diagnosed in an advanced stage (75%). Moreover, 14.6% had precancerous conditions, and the *H. pylori* infection rate was 68.4%. In patients with primary gastric lymphoma, GC occurred mostly in *H. pylori*-infected patients (95.8%) and rarely after *H. pylori* eradication (4.2%).

The overall success rate for *H. pylori* eradication was 87.1%, with no difference in MALT lymphoma (89.9%), DLBCL (88.3%), and other pathological types (84.6%). These results point out the relevance of adequate endoscopic inspection, both in the lymphoma first diagnostic endoscopy and the further endoscopic surveillance exams of primary gastric lymphoma patients, and the relevance of *H. pylori* eradication to prevent progression to metachronous GC.

GASTRIC CANCER SCREENING IN WESTERN COUNTRIES

Farinati et al[26] published a review article regarding the specificities of gastric cancer in Western countries. The article described the available primary and secondary preventive measures and discussed the opportunity to introduce screening in Western countries.

H. pylori screening and treatment (primary prevention), as well as endoscopic surveillance (secondary prevention), can lead to a progressive drop in GC mortality of 10 %. Prospective and observational studies demonstrate the ability of endoscopic screening to reduce GC mortality[5,27-29].

Primary prevention can be performed by vitamin intake, dietary restrictions, alcohol and smoking reduction, or *H. pylori* eradication[30]. Patients receiving *H. pylori* eradication have a lower risk of developing GC (RR 0.54, 95 % CI: 0.40-0.72) and a reduction in GC mortality (RR 0.61, 95 % CI: 0.40-0.92)[31]. As so, both the World Health Organization and the Maastricht VI/Florence consensus endorsed population screening for *H. pylori* to prevent GC[32,33].

Secondary prevention can be performed by endoscopic surveillance of precancerous conditions in the stomach, by performing an upper gastrointestinal endoscopy every 3 years in patients with: AG or IM that involves both antrum and corpus (OLGA/OLGIM III and IV stages), (every 1-2 years if the patient has a family history of GC), AG or IM restricted to the antrum or corpus with a family history of GC, incomplete IM, or persistent *H. pylori* infection[4]. In Europe, endoscopic screening proved to be cost-effective when combined with a colonoscopy performed for colorectal screening for an incidence of GC ≥10/100,000/year[5].

CONCLUSIONS

The relation between *Helicobacter pylori* infection and gastric precancerous conditions or lesions continues to provide new evidence every year. In the near future, updated evidence regarding reversal of conditions after *Helicobacter pylori* eradication, and gastric endoscopic screening combined with colorectal screening are expected.

Conflict of Interest

The authors have no conflicts of interest to declare.

Acknowledgments

None.

Informed Consent

Not applicable. This is a review article without the inclusion of patients.

Authors' Contribution

All authors contributed equally to this paper, including conception, data collection, and writing the manuscript. All authors read and approved the final version.

Funding

None.

ORCID ID

Areia M: 0000-0001-9787-8175
Dinis-Ribeiro M: 0000-0003-0121-6850

AI Disclosure

No artificial intelligence was used in the draft of the manuscript.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71: 209-249.
2. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984; 1: 1311-1315.
3. Correa P, Haenszel W, Cuello C, Tannenbaum S, Archer M. A model for gastric cancer epidemiology. Lancet 1975; 2: 58-60.
4. Pimentel-Nunes P, Libanio D, Marcos-Pinto R, Areia M, Leja M, Esposito G, Garrido M, Kikuste I, Megraud F, Matysiak-Budnik T, Annibale B, Dumonceau JM, Barros R, Flejou JF, Carneiro F, van Hooft JE, Kuipers EJ, Dinis-Ribeiro M. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy 2019; 51: 365-388.
5. Areia M, Spaander MC, Kuipers EJ, Dinis-Ribeiro M. Endoscopic screening for gastric cancer: A cost-utility analysis for countries with an intermediate gastric cancer risk. United European Gastroenterol J 2018; 6: 192-202.
6. Liang Y, Yang Y, Nong R, Huang H, Chen X, Deng Y, Huang Z, Huang J, Cheng C, Ji M, Chen Y, Hu F. Do atrophic gastritis and intestinal metaplasia reverse after *Helicobacter pylori* eradication? Helicobacter 2024; 29: e13042.
7. Zou TH, Gao QY, Liu S, Li YQ, Meng XJ, Zhang GX, Tian ZB, Zou XP, He S, Hou XH, Lin R, Li JN, Zhou ZY, Li Y, Wang MC, Wang BM, Tian A, Chen SJ, Cao Q, Li LP, Wang ZR, Shen XZ, Liu BR, Yan XY, Chen YX, Fang JY. Effectiveness and safety of Moluodan in the treatment of precancerous lesions of gastric cancer: A randomized clinical trial. J Dig Dis 2024; 25: 27-35.
8. Wang YM, Luo ZW, Shu YL, Zhou X, Wang LQ, Liang CH, Wu CQ, Li CP. Effects of *Helicobacter pylori* and Moluodan on the Wnt/beta-catenin signaling pathway in mice with precancerous gastric cancer lesions. World J Gastrointest Oncol 2024; 16: 979-990.
9. Carlosama YH, Acosta CP, Sierra CH, Rosero CY, Bolanos HJ. The Operative Link on Gastritis Assessment (OLGA) system as a marker for gastric cancer and dysplasia in a Colombian population at risk: A multicenter study. Biomedica 2023; 43: 30-40.
10. Sugano K, Moss SF, Kuipers EJ. Gastric Intestinal Metaplasia: Real Culprit or Innocent Bystander as a Precancerous Condition for Gastric Cancer? Gastroenterology 2023; 165: 1352-1366.e1351.
11. Capelle LG, de Vries AC, Haringsma J, Ter Borg F, de Vries RA, Bruno MJ, van Dekken H, Meijer J, van Grieken NC, Kuipers EJ. The staging of gastritis with the OLGA system by using intestinal metaplasia as an accurate alternative for atrophic gastritis. Gastrointest Endosc 2010; 71: 1150-1158.
12. Shah SC, Gawron AJ, Mustafa RA, Piazuelo MB. Histologic Subtyping of Gastric Intestinal Metaplasia: Overview and Considerations for Clinical Practice. Gastroenterology 2020; 158: 745-750.
13. Banks M, Graham D, Jansen M, Gotoda T, Coda S, di Pietro M, Uedo N, Bhandari P, Pritchard DM, Kuipers EJ, Rodriguez-Justo M, Novelli MR, Ragunath K, Shepherd N, Dinis-Ribeiro M. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. Gut 2019; 68: 1545-1575.
14. Shah SC, Piazuelo MB, Kuipers EJ, Li D. AGA Clinical Practice Update on the Diagnosis and Management of Atrophic Gastritis: Expert Review. Gastroenterology 2021; 161: 1325-1332 e1327.
15. Li ML, Hong XX, Zhang WJ, Liang YZ, Cai TT, Xu YF, Pan HF, Kang JY, Guo SJ, Li HW. *Helicobacter pylori* plays a key role in gastric adenocarcinoma induced by spasmolytic polypeptide-expressing metaplasia. World J Clin Cases 2023; 11: 3714-3724.
16. Petersen CP, Weis VG, Nam KT, Sousa JF, Fingleton B, Goldenring JR. Macrophages promote progression of spasmolytic polypeptide-expressing metaplasia after acute loss of parietal cells. Gastroenterology 2014; 146: 1727-1738. e1728.
17. Chong Y, Yu D, Lu Z, Nie F. Role and research progress of spasmolytic polypeptide-expressing metaplasia in gastric cancer (Review). Int J Oncol 2024; 64: 33.
18. Caldwell B, Meyer AR, Weis JA, Engevik AC, Choi E. Chief cell plasticity is the origin of metaplasia following acute injury in the stomach mucosa. Gut 2022; 71: 1068-1077.

19. Mills JC, Goldenring JR. Metaplasia in the Stomach Arises From Gastric Chief Cells. Cell Mol Gastroenterol Hepatol 2017; 4: 85-88.
20. Nguyen DTN, Quach DT, Le QD, Vu NTH, Dang NLB, Le HM, Le NQ, Oka S, Tanaka S, Hiyama T. Endoscopic Kyoto and Kimura-Takemoto Classifications Are Comparable in Predicting High-Risk Gastric Precancerous Lesions. Digestion 2024; 105: 140-148.
21. Ferrari F, Ogata DC, Mello CAL. Role of Incisura Angularis Biopsy in Gastritis Staging and Risk Assessment of Gastric Cancer. Arq Gastroenterol 2023; 60: 478-489.
22. Jang B, Kim H, Lee SH, Won Y, Kaji I, Coffey RJ, Choi E, Goldenring JR. Dynamic tuft cell expansion during gastric metaplasia and dysplasia. J Pathol Clin Res 2024; 10: e352.
23. Strine MS, Wilen CB. Tuft cells are key mediators of interkingdom interactions at mucosal barrier surfaces. PLoS Pathog 2022; 18: e1010318.
24. Feng Y, Duan TJ, Huang Q, Li ZY, Liu YP, Luo MS, Lu GF, Shi W, Zhang ZY, Li HX. The clinicopathological characteristics of gastric cancer and precancerous conditions in gastric DLBCL and MALT lymphoma patients: a multi-center retrospective study. Ann Med 2023; 55: 2193423.
25. Paydas S. *Helicobacter pylori* eradication in gastric diffuse large B cell lymphoma. World J Gastroenterol 2015; 21: 3773-3776.
26. Farinati F, Pelizzaro F. Gastric cancer screening in Western countries: A call to action. Dig Liver Dis 2024: S1590-8658(24)00269-X. doi: 10.1016/j.dld.2024.02.008. Epub ahead of print.
27. Asaka M, Kato M, Sakamoto N. Roadmap to eliminate gastric cancer with *Helicobacter pylori* eradication and consecutive surveillance in Japan. J Gastroenterol 2014; 49: 1-8.
28. Mabe K, Inoue K, Kamada T, Kato K, Kato M, Haruma K. Endoscopic screening for gastric cancer in Japan: Current status and future perspectives. Dig Endosc 2022; 34: 412-419.
29. Kim H, Hwang Y, Sung H, Jang J, Ahn C, Kim SG, Yoo KY, Park SK. Effectiveness of Gastric Cancer Screening on Gastric Cancer Incidence and Mortality in a Community-Based Prospective Cohort. Cancer Res Treat 2018; 50: 582-589.
30. Song Y, Liu X, Cheng W, Li H, Zhang D. The global, regional and national burden of stomach cancer and its attributable risk factors from 1990 to 2019. Sci Rep 2022; 12: 11542.
31. Ford AC, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer: systematic review and meta-analysis. Gut 2020; 69: 2113-2121.
32. International Agency for Research on Cancer (IARC). *Helicobacter pylori* eradication as a strategy for preventing gastric cancer. Lyon: International Agency for Research on Cancer: 2014.
33. Malfertheiner P, Megraud F, Rokkas T, Gisbert JP, Liou JM, Schulz C, Gasbarrini A, Hunt RH, Leja M, O'Morain C, Rugge M, Suerbaum S, Tilg H, Sugano K, El-Omar EM; European Helicobacter and Microbiota Study group. Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report. Gut 2022: gutjnl-2022-327745. doi: 10.1136/gutjnl-2022-327745. Epub ahead of print.