KJHUGR REVIEW
pISSN 1738-3331 / eISSN 2671-826X https://doi.org/10.7704/kjhugr.2026.0027 Korean J Helicobacter Up Gastrointest Res 2026;26(3):265-274

https://www.helicojournal.org

Received March 31, 2026
Revised May 6, 2026
Accepted May 19, 2026

Corresponding author
Massimo Rugge, MD, FACG
Department of Medicine - DIMED,
Anatomic Pathology and
Cytopathology Unit,
University of Padova Italy,
Via Aristide Gabelli, 61,
Padova 35121, Italy
E-mail: massimo.rugge@unipd.it

Availability of Data and Material
Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

Conflicts of Interest
Massimo Rugge, a contributing editor of the *Korean Journal of Helicobacter and Upper Gastrointestinal Research*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Funding Statement
None

Acknowledgements
None

Gastric Mucosa Cancer Risk: The Operative Link on Gastritis Assessment Staging System

Massimo Rugge[1,2], Marta Sbaraglia[1], Giulia Fiorini[3,4], Gavino Faa[5,6], and Robert M Genta[2,7]

[1]Department of Medicine - DIMED, Anatomic Pathology and Cytopathology Unit, University of Padova Italy, Padova, Italy
[2]Departments of Pathology and Medicine, Baylor College of Medicine, Houston, TX, USA
[3]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
[4]Cardiovascular Medicine Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy
[5]Department of Medical Sciences and Public Health, University of Cagliari and AOU of Cagliari, Cagliari, Italy
[6]Department of Biology, College of Science and Technology, Temple University, Philadelphia, PA, USA
[7]Unilabs Pathologie, Geneva, Switzerland

Gastric mucosa atrophy is the cancerization field for gastric cancer development. Atrophic changes in the gastric mucosa can be assessed endoscopically and histologically. Gastric serology (e.g., pepsinogens and their ratio, and gastrin) may provide information on the functional status of the mucosa. However, outside large-scale epidemiological studies, the clinical reliability of serology at the individual patient level remains controversial. Histology-based estimates of atrophy-associated neoplastic risk require mucosal specimens from both the antral/mucus-secreting and corpus/fundus oxyntic compartments. Inspired by the clinical–biological framework of cancer staging, the Operative Link on Gastritis Assessment (OLGA) staging system classifies the severity and topography of mucosal atrophy into five stages, ranging from 0 to IV. International trials have validated the stepwise increasing risk of cancer with disease progression. Based on this evidence, OLGA stages are classified into low-risk (0–I) and high-risk (III–IV), with stage II remaining clinically controversial. The prevalence of high-risk stages varies according to patient- and population-specific risk factors. Among these, the most significant is the prevalence of *Helicobacter pylori*, a recognized oncogenic agent. Bacterial infection at the time of the initial endoscopy requires eradication therapy regardless of the stage of gastritis. Histological stage reliably identifies the endoscopic population at a high risk of cancer progression and shapes the schedule of endoscopy/histology-based surveillance. Serology at the index endoscopy may circumvent the inherent inconsistencies of population-based studies. This patient-specific serology could serve as an interval for non-invasive monitoring within the endoscopy/histology follow-up framework.

Keywords Gastric cancer; *Helicobacter pylori*; OLGA staging; Gastric cancer prevention; Atrophic gastritis.

INTRODUCTION

Under normal conditions, the lamina propria of the gastric mucosa hosts a few resident lymphocytes, histiocytes, rare plasmacytes, and extremely rare or no polymorphs.[1] Gastritis is defined as the microscopic presence of a leukocyte population exceeding the resident component.

Dyspepsia is the most common presentation of gastritis, ranging from minimal epigastric-centered discomfort to alarming symptoms such as vomiting or bleeding.[2] In such

cases, esophagogastroduodenoscopy (EGD) is commonly recommended along with gastric mucosal biopsy.

Gastric serology includes testing of gastric mucosal functions (e.g., pepsinogens and gastrin), *Helicobacter pylor*i status, and gastric autoimmunity. Pepsinogen 1 (Pg-1) is mainly secreted by the oxyntic glands, whereas Pg-2 is secreted by all the gastric and proximal duodenal Brunner's glands. Pepsinogen secretion may be affected by inflammatory conditions (e.g., *H. pylori* infection),[3] atrophic-metaplastic transformation of the gastric lining, or both.[4-9] Gastrin 17 is the most abundant circulating gastrin peptide produced by neuroendocrine antral G cells targeting oxyntic enterochromaffin-like cells (ECL) and parietal cells and promotes acid secretion. Increased G17 levels are associated with gastric hypo- or achlorhydria.[5] Circulating antibodies may provide information on previous or current *H. pylori*-positive status. Clinical suspicion of autoimmune gastritis (AIG) can be confirmed by the serological detection of autoantibodies against anti-parietal cells and anti-intrinsic factors.[10-14] Active *H. pylori* infection can be confidently diagnosed using the urea breath test (13C-UBT) and *H. pylori* stool antigen detection.[3,15-17]

The etiology is the most reliable reference for the classification of gastritis.[18] The World Health Organization distinguishes between communicable and noncommunicable etiological agents.[19] Both etiologies may result in self-limiting and non-self-limiting inflammatory lesions. Worldwide, longstanding (i.e., chronic), non-self-limiting gastritis is primarily caused by *H. pylori* infection.[20] The second most common cause is a cytolytic T cell-mediated attack on gastric parietal cells (AIG), with a significantly lower prevalence than that of *H. pylori* infection.[21-24]

Long-standing gastric mucosal inflammation may lead to epigenetic and genetic molecular disarrays, impaired mucosal function, and microscopic disarrangement of the gastric lining. The combination of these inflammation-driven conditions creates a "field of cancerization" that can cause and enable the progression to gastric cancer (GC). The microscopic hallmark of this GC-promoting condition is the loss of native gastric glands, which is commonly recognized as "mucosal atrophy."[25-27]

Irrespective of its etiology, the cancerization field topographically involves the gastric mucosa far beyond the focal area, where precancer or cancer lesions may become endoscopically/histologically detectable.[28-31] Any histological assessment of atrophy should comprehensively consider 1) the topographical extent of the cancer-prone mucosa and 2) the microscopic spectrum of atrophy phenotypes involved in cancer promotion.

This review focuses on the clinical priority of histological reporting of atrophy in gastric biopsy specimens. Histological staging of gastric mucosal atrophy provides clinicians with an easily accessible diagnostic information on the risk of GC tailored to patient-specific gastric conditions.

Twenty years ago, inspired by staging systems applied in oncology or inflammatory liver diseases,[31] an international group of gastroenterologists and pathologists (Operative Link on Gastritis Assessment [OLGA]) proposed a framework (OLGA system) for staging gastric mucosal atrophy.[32-34] The disease stage was used to determine the severity of atrophy and its associated GC risk. Building on the original OLGA staging proposal, other staging systems have been suggested for the endoscopic or histological assessment of atrophy.

CLASSIFICATION OF GASTRITIS BASED ON ETIOLOGY, CLINICAL COURSE, MUCOSAL ATROPHY

More than a nosological exercise, the classification of gastritis provides clinically important information regarding diagnostic workup, treatment, and patient monitoring.

The etiology-based classification of gastritis includes environmental (i.e., communicable/transmissible) and host-related (non-communicable/non-transmissible) factors (Table 1). Based on the clinical presentation (i.e., symptoms and signs), gastritis is usually classified as either non-self-limited (commonly called "chronic" or "long-standing") or self-limited. The latter is mostly characterized by sudden-onset and quickly remitting dyspeptic symptoms (clinically defined as "acute"). From a histological perspective, the cellular component of the inflammatory population may not correspond to the traditional, so-called "acute" (predominantly neutrophilic polymorphonuclear cells) versus "chronic" (mononuclear cells predominate) gastritis, and such a histological definition should be discouraged.

Histologically, gastritis is classified into two main categories: non-atrophic and atrophic, the latter being associated with an increased risk of GC.[27,35] Histological reporting of gastric mucosal atrophy requires distinguishing atrophic changes according to the gastric compartment in which they occur, specifically the corpus/fundus (oxyntic) or the antrum/angulus (mucus-secreting). Coexisting inflammatory lesions present a distinct diagnostic message, supported by the semantic distinction between "gastritis" and non-inflammatory gastric mucosal lesions. Lymphocytic/plasmacytic infiltrates should be graded semi-quantitatively as low or high-grade. The polymorphonuclear cell infiltrate should be reported, indicating whether detected in the lamina propria, glandular lumen, or inter-epithelial spaces (all these lesions are usually defined as "activity," see below).

 https://doi.org/10.7704/kjhugr.2026.0027

Table 1. Etiological classification of gastritis includes environmental agents and host-related conditions

Etiological category		Etiological agents
Environmental, due to communicable agents	Parasites	*Ansakis*
		Cryptosporidium
		Strongyloides stercoralis
	Micetes	*Candida*
		Histoplasma capsulatum
		Rhizopus arrhizus
	Bacteria	*Actinomyces*
		Clostridium perfringens
		Enterobacteriaceae
		Helicobacter pylori (potential atrophy promoter and trigger of autoimmune oxyntic-targeted reaction)
		Non-Helicobacter pylori Helicobacter species (potential atrophy promoters)
		Mycobacterium avium tuberculosis, atypical
		Pseudomonas aeruginosa
		Staphylococcus aureus
		Treponema pallidum
	Virus	*Coronaviridae* (i.e., SARS-CoV-2)
		Picornaviridae (including different species of *Enterovirus*)
		Herpesviridae (e.g., *Cytomegalovirus*, Epstein-Barr virus)
Environmental, due to non-communicable agents	Exogenous chemical agents	Doxycycline, Iron pill, Kayexalate in sorbitol, Lanthanum carbonate, non-steroidal anti-inflammatory drugs, Taxol
	Physics	Radiation
Host-related (due to non-communicable etiology)	Immunomediated etiology (identified by the diagnostic definition of the autoimmune disease)	Autoimmune oxyntic-restricted gastritis ([AIG] non-atrophic or atrophic)
		Autoimmune gastritis with variable gastric involvement in extra-gastric autoimmune conditions (e.g., Autoimmune Enteropathy, Autoimmune Thyroiditis, Celiac Disease, Crohn's Disease, IgG4-related Disease, Lupus Erythematosus, Systemic Sclerosis, Sarcoidosis, Sjögren Syndrome, Ulcerative Colitis)
		Autoimmune pan-gastritis in multiorgan autoimmunity
		Gastritis associated to therapy with immune checkpoint inhibitors
		Gastritis in graft-versus-host diseases
		So-called "special forms" of gastritis (e.g., Collagenous, Lymphocytic, Eosinophilic)

Environmental factors (*H. pylori*) may trigger gastric autoimmunity (AIG). Some chemical agents, either endogenous (e.g., bile reflux into the stomach) or exogenous (e.g., lanthanum), can cause mucosal gastric abnormalities with negligible inflammatory component (so called "reactive gastropathies").

GASTRITIS: THE HISTOLOGICAL PHENOTYPES

Damage to the gastric mucosa can be classified into non-atrophic and atrophic types, based on the population of native glandular units. This dichotomous distinction influences the risk of GC. Both atrophic and non-atrophic mucosa may co-exist with inflammatory lesions.

Atrophic transformation encompasses a spectrum of microscopic phenotypes that differ depending on the pathology of the gastric compartment in which they occur. A detailed description of the biology of atrophy is beyond the scope of this review; however, a few details on this "technical issue" may promote communication among pathologists, gastroenterologists, and medical practitioners.

Gastric mucosal atrophy is defined as the loss of gastric glands appropriate for the oxyntic (corpus/fundus) and mucus-secreting antral/pyloric stomach down to the incisura angularis.

The phenotypes of atrophy include: 1) shrinkage or complete disappearance of glandular units replaced by fibrotic lamina propria. This reduces the glandular mass without modify-

ing the original cell phenotype; 2) replacement of native glands with metaplastic glands featuring a new commitment (i.e., intestinal [IM] and/or pseudo-pyloric metaplasia [PPM]). The number of glandular units is not necessarily lower, but the metaplastic replacement of the native glandular population results in fewer glandular structures being "appropriate" for the compartment concerned (i.e., oxyntic glandular units in the proximal stomach and mucus-secreting glands in the distal compartment, down to the incisura angularis). The metaplastic replacement of native glandular units results in the morpho-functional "loss of the appropriate glands." There are two main types of gastric metaplasia.

PPM replaces a native population of oxyntic glands, which is consistent with the comprehensive definition of gastric mucosal atrophy.[36-38] The pseudopyloric epithelium is marked by the immunohistochemical expression of trefoil factor 2.[39] The spotty expression of Pg-1 revealed native oxyntic commitment of the pseudo-pyloric glands.[39] Clinical and molecular studies have explored the potential of PPM in GC progression. Their conclusions can be summarized as follows: 1) in experimental models, the spasmolytic polypeptide-expressing metaplasia (SPEM)-related molecular profile has potential for cancer evolution[40]; 2) in humans, PPM can be confidently considered as the morphological counterpart of the SPEM's molecular profile[41]; 3) the loss of oxyntic Pg-1-producing cells leads to the "PPM-atrophic subtype"[42]; and 4) experimental and clinical studies support the hypothesis that PPM may either undergo to further modification acquiring the phenotype of intestinal epithelia,[43] or coexists with glands' intestinalization.[44,45]

Intestinal metaplasia (IM) may develop in native mucus-secreting (antral) epithelia or antral oxyntic glands (i.e., PPM). Different IM subtypes have been distinguished based on whether the metaplastic epithelium phenotype more closely resembles that of the colon ("incomplete" or colonic-type intestinal metaplasia; so-called Type I-III IM) or that of the small intestine ("complete," Type I IM). Histologically proven colonic metaplasia identifies stomachs that are at risk of cancer development. Given the significant correlation between the score for the incomplete-type IM and its total extent, IM subtyping is primarily applied in research settings rather than in clinical practice.[46] Recent data have linked small intestinal-type IM to the atrophic pattern of AIG.[47-49]

Globally, at least 90% of GC cases originate from atrophic gastritis. An increased risk of GC is also associated with successfully eradicated patients who harbor extensive (high-stage) cancer-promoting mucosal atrophy, which persists after *H. pylori* eradication.[12,49-51] In these patients, morpho-functional atrophic transformation results in a combination of cancer-promoting changes, including DNA toxicity, modifications of the cytokine cascade, oxidative damage, and cancer-prone remodulation of the native microbiota.[52,53]

The chronological sequence and the oncogenic impact of these events in the GC "cascade" are only partially known. However, the occurrence of GC in patients who develop atrophic changes before bacterial eradication suggests an increased atrophy-specific cancer risk even after the infection is cured.[54] From a clinical perspective, this evidence supports the continued surveillance of patients with extensive atrophy, even after the successful eradication of *H. pylori*.[51]

GASTRITIS OLGA STAGING IN CLINICAL PRACTICE

The clinical importance of OLGA staging lies in its ability to accurately predict GC risk. However, regardless of the stage of gastritis, all *H. pylori*-positive patients benefit from the bacterial eradication.[2,12]

Table 2 outlines the histological criteria used to assess the

Table 2. OLGA system for gastritis staging

Atrophy score (G=grade) in the whole set of the biopsy specimens obtained from the same mucosal compartment: G0=no atrophy (any histological subtype) G1=atrophy involving 1%–30%(any histological subtype) G2=atrophy involving 31%–60% (any histological subtype) G3=atrophy involving >60% (any histological subtype)		Corpus/fundus biopsy specimens Atrophy score (G) assessed in the whole set of biopsy samples from corpus/fundus mucosa			
		Score G0	Score G1	Score G2	Score G3
Antrum/angularis biopsy specimens Atrophy score (G) assessed in the whole set of biopsy samples from the antrum and angularis incisura	Score G0	STAGE 0	STAGE I	STAGE II	STAGE II
	Score G1	STAGE I	STAGE I	STAGE II	STAGE III
	Score G2	STAGE II	STAGE II	STAGE III	STAGE IV
	Score G3	STAGE III	STAGE III	STAGE IV	STAGE IV

Atrophy scores (G0, G1, G2, G3) indicate percentages of atrophic changes (both non-metaplastic and metaplastic [IM and PPM]). Atrophy is scored as "overall percentage" across a set of biopsy samples taken from the same mucosal compartment (mucus-secreting: antral/angularis versus oxyntic: corpus/fundic). In red: stages at high GC risk.
OLGA, Operative Link on Gastritis Assessment; IM, intestinal metaplasia; PPM, pseudo-pyloric metaplasia; GC, gastric cancer.

 https://doi.org/10.7704/kjhugr.2026.0027

OLGA stages. Based on their associated risk of cancer progression, stages 0, I, and II are considered to have a low GC risk, whereas Stages III and IV are associated with an increased risk of cancer progression. Histological assessment of the OLGA stage involves the following steps: 1) obtain a biopsy set compliant with the Houston-Updated Sydney system, representative of the oxyntic and mucus-secreting gastric compartments; 2) submit the biopsy samples in at least two separate vials, each labeled according to the compartment (antrum/incisura angularis versus corpus fundus) from which they were obtained. Any focal lesion must be targeted by an additional biopsy sampling t and submitted to separate topographically labeled vials; 3) comprehensively score of all the atrophy subtypes by the gastric mucosal compartment; and 4) combine atrophy scores from the corpus/fundus and antral/angular compartments and combine them in the final stage, ranging from 0 to IV.

In some cases, due to the inconsistency in sampling or tissue orientation, OLGA staging may be deferred.

The first two actions are the responsibility of the endoscopist, while steps three and four fall under the responsibility of the pathologist.

Steps 1 & 2: based on embryonic patterning, the stomach is described as "two organs in one sac."[55] This dual mucosal commitment leads to distinct pathophysiological changes in the oxyntic/proximal and the mucus-secreting/distal stomach mucosa. The two main models of atrophy highlight the diversity of the gastric mucosa.

In the natural history of *H. pylori* infection, inflammation and atrophy initially affect the mucus-secreting mucosa, progressing to the oxyntic stomach as the disease advances.[56,57]

In AIG, lesions are restricted to the oxyntic stomach.[43,58] The diagnostic impact of the topographic distribution of atrophy results in three major recommendations (Table 2): a) obtain two biopsy samples from the oxyntic mucosa, one targeting the anterior wall and one targeting the greatest curvature; b) obtain a biopsy sample from the transitional mucosa between the corpus and antral mucosa (incisura angularis zone along the lesser curvature); and c) obtain two biopsy samples from the mucus-secreting/distal stomach down the incisura angularis. The samples identified as "a" and those "b and c" should be submitted in separate vials, labeled by biopsy site. Distinguishing "a" from "b" biopsy specimens would be desirable. The sampling protocol must include any occasional focal lesion(s), which should be submitted in a separate vial and identified by its/their mucosal topography.

Steps 3 & 4 cover the microscopic assessment of atrophic/inflammatory lesions and the formatting of the diagnostic report. While the histological assessment of the atrophy score is performed by pathologists, gastroenterologists and endoscopists should be aware of the extent to which the quality of biopsy sampling affects the reliability of staging. The atrophy grade is assessed microscopically in biopsy samples from the overall antral/angular biopsy set and the corpus/fundus specimens. The atrophy score encompasses all phenotypic changes (non-metaplastic and metaplastic [IM and PPM]). In both the oxyntic and mucus-secreting compartments, the score values range from zero (no atrophy: grade=0) to more than 60% (atrophy score grade=3; Table 2). The combination of atrophy grades from the two gastric compartments determined the OLGA stage, which ranged from 0 to IV (Table 2). The atrophy stage is independent of the assessment of any coexisting inflammatory component (i.e., gastritis), which represents an adjunctive diagnostic parameter. In each compartment, inflammation was scored as absent, low, or high. The explicit distinction between inflammation and atrophy scores is crucial in *H. pylori*-associated diseases, where minimal inflammation may persist after the successful eradication of *H. pylori*.[12,22,27]

In routine diagnostic practice, high-grade inflammatory lesions (primarily associated with *Helicobacter pylor*i infection) or inconsistent orientation of biopsy specimens can present challenges in the assessment of atrophy. This "indefinite for atrophy" phenotype should prompt the deferral of the OLGA stage assessment until post-eradication follow-up or until a new set of biopsies is obtained, when clinically indicated.[27]

Based on this, the diagnostic report should include[21]: 1) the distinction between non-atrophic and atrophic mucosal damage; 2) reporting the atrophy grades (e.g., G0, G1, G2, and G3), distinguishing the corpus/fundus and antrum/angulus biopsies (e.g., antral atrophy score=Gx; corpus/fundus atrophy score=Gx), and their resulting OLGA stage (Fig. 1, Table 2); 3) the distinct score of inflammation and gastritis "activity"; and 4) a plausible etiological hypothesis based on the gastritis histological phenotype.

Capelle et al.[32] suggested an alternative staging format. Their proposal replaces the original OLGA-atrophy score (including non-metaplastic, and metaplastic subtypes) with a simplified scoring system limited to IM. By reducing the histological variables considered by the OLGA-staging, the Operative Link on Gastric Intestinal Metaplasia assessment (OLGIM) system has been reported to achieve higher interobserver consistency, while potentially affecting the accuracy of GC risk estimates.[32,59-62]

The Operative Link on Gastric Intestinal metaplasia and Glandular Atrophy Assessment (OLGIMA) system is the most recently proposed staging system.[63] By excluding PPM from the atrophy score, staging relies exclusively on non-metaplastic and IM atrophic changes. As for the OLGA and OLGIM

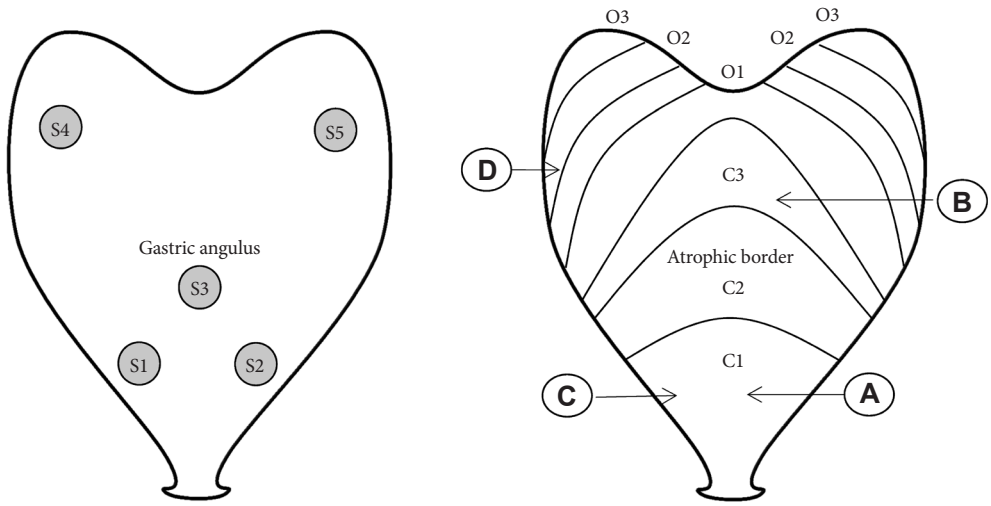

Fig. 1. Obtaining gastric biopsy samples for diagnostic purposes. The stomach is opened along the greater curvature. Biopsy sampling protocol suggested by the updated Sydney System (left). The system recommends obtaining biopsy samples from the antral (S1–S2), angular (S3), and oxyntic (S4–S5) mucosa. According to OLGA staging, the histological severity of overall atrophic changes is scored as the mean atrophy percentage in the antral/incisural (S1–S3) and body/fundus mucosa (S4–S5). In Eastern Asian clinical practice, the assessment of gastric atrophy primarily focuses on the cranial movement of the "atrophic border." This border marks the transition between the most caudal oxyntic mucosa and the most cranial mucosecreting mucosa, as described by Kimura–Takemoto.[29] The endoscopic severity of atrophy is ranked as mild (C1, C2), moderate (C3, O1), and severe (O2, O3); the most informative biopsy samples should be obtained from sites A, B, C, and D (on the right). OLGA, Operative Link on Gastritis Assessment.

systems, OLGIMA stages III and IV were associated with increased GC risk. The reproducibility and clinical significance of the OLGIMA system have not been evaluated outside the proposing centers.

The similarities and differences between the OLGA and OLGIM staging systems can be summarized as follows.

- Both systems use a Sydney-based protocol for biopsy sampling and recommend submitting the specimens separate vials.[64]

- Both systems recognize histologically assessed mucosal atrophy as a key factor affecting GC risk estimates; however, they differ in their definition of atrophy.

- Both systems require structured training and operator expertise.[65]

- Both systems aim to convey a straightforward message to guide patient management. The differences in the phenotypic variables included in the atrophy scores of OLGA and OLGIM lead to distinct advantages: 1) OLGIM's IM-restricted atrophy assessment increases inter-observer consistency; 2) OLGA's inclusion of a broader spectrum of atrophy phenotypes expands the estimates of high-risk gastritis stages.[66] In a retrospective analysis of 4556 cases, 5.8% of high-risk OLGA stages were reclassified as low risk according to the OLGIM criteria. Isajevs and colleagues compared the interobserver agreement and prognostic performance of the OLGA and OLGIM systems in a cohort of 836 patients. The authors' conclusions were as follows: "OLGIM staging provided the highest interobserver agreement, but a substantial proportion of potentially high-risk individuals would be missed if only OLGIM staging is applied."[60,67] Other studies comparing case distributions between the two systems found that a substantial number of cases were staged lower by OLGA than by OLGIM, which is surprising given the broader spectrum of atrophic changes included in the OLGA atrophy score.[68-70]

- Both systems significantly predict the risk of metachronous GC after endoscopic submucosal dissection for early GC.[71]

- Neither system includes information about coexisting inflammation, which should be graded separately.

OLGA STAGING IN CANCER RISK PREDICTION

International prospective and retrospective studies conducted in various epidemiological settings have supported the different cancer risks associated with each OLGA stage. Table 3 summarizes the results of two long-term follow-up studies involving 9191 consecutive endoscopy patients.[72,73] In follow-ups >50 months, both studies found that OLGA stages III and IV (i.e., high-risk stages) were associated with a significantly increased risk of developing neoplastic lesions. Conversely, the same studies reported a significantly lower risk of neoplasms, including intraepithelial neoplasia or invasive GC, in stages 0-I-II (low-risk stages).

In a study involving 7436 consecutive patients,[72] multivariate analysis, including sex, age, OLGA stage, and *H. pylori* status at presentation, showed only the histological stage signifi-

 https://doi.org/10.7704/kjhugr.2026.0027

Table 3. Risk of incident gastric neoplasia (either non-invasive [synonym intraepithelial neoplasia] or invasive adenocarcinoma [GC]) by gastritis OLGA staging

Prevalence of OLGA stage at enrollment	Incident neoplasia (absolute number)	Incident of neoplasia rate/10^3 person years	Follow-up time
Overall patients 7436[72]	LG-IEN=17 HG-IEN=4 GC=7		Years mean/median=6.3/6.6
Stage 0: 80.8%	1/6005	0.03 (95% CI: 0.004–0.19)	Years mean/median=6.3/6.6
Stage I: 12.6%	2/934	0.34 (95% CI: 0.09–1.36)	Years mean/median=6.3/6.6
Stage II: 4.3%	3/322	1.48 (95% CI: 0.48–4.58)	Years mean/median=6.3/6.6
Stage III: 2.0%	17/152	19.1 (95% CI: 11.9–30.7)	Years mean/median=5.9/6.2
Stage IV: 0.3%	5/23	41.2 (95% CI: 17.2–99.3)	Years mean/median=5.3/6.3
Overall patients 1755[73]	LG-IEN=4 HG-IEN=1 GC=2		Mean/median months=52.7/54.9 (r: 11.5–73.0)
Stage 0: 77.6%	0/1362	0/0 (olny clinical FU)	Mean months=53.6 (r: 11.5–73.0)
Stage I: 14.4%	0/253		
Stage II: 5.1%	0/88	0/0	Mean months=38.6 (r: 5.9–64.3)
Stage III: 2.1%	4/37	36.5 (95% CI: 13.7–97.4)	Mean months=35.5 (r: 15.8–60.7)
Stage IV: 0.85%	3/15	63.1 (95% CI: 20.3–195.6)	Mean months=39.4 (r: 23.3–58.1)

Both studies show non-significant neoplastic risk in stages 0-1-II (low-risk stages). Significant GC risks are associated with Stages III-IV (high-risk stages).
OLGA, Operative Link on Gastritis Assessment; LG-IEN, low-grade intraepithelial neoplasia; HG-IEN, high-grade intraepithelial neoplasia; GC, gastric cancer; CI, confidence interval; r, range; FU, follow-up.

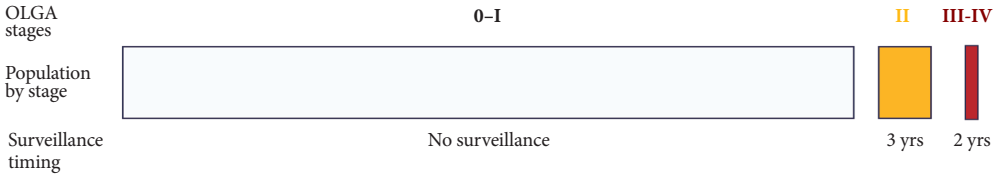

Fig. 2. Prevalence of OLGA stages (0-IV) in an endoscopic population recruited in an epidemiological study with low to medium gastric cancer risk. The distribution of patients by stage (percentage) is represented by the length of the bars. Surveillance (including endoscopy and histological follow-up) is guided by histology in *H. pylori*-negative patients (whether naïve or eradicated) according to OLGA stage. This occurs when there are no accompanying endoscopic, demographic (such as sex, age, or family history of gastric cancer), or biological risk factors (such as the predominance of incomplete-type intestinal metaplasia, etc.). OLGA, Operative Link on Gastritis Assessment.

cantly linked to neoplastic progression (hazard ratios: Stage O=1; Stage I=12.7 [1.14–140.7]; Stage II=54.9 [5.63–534.6]; Stage III=712.4 [92.5–5484.5]; Stage IV: 1450 [166.7–12626]). Based on the above-mentioned experience, the low prevalence of stages III and IV (2.3% in endoscopic cohorts, increasing to 6.6% when stage II is included) supports the feasibility of effectively implementing secondary prevention strategies that combine esophagogastroduodenoscopy with appropriate biopsy sampling.[16,74] For *H. pylori*-negative patients (either naïve or previously eradicated), Fig. 2 provides a timing framework for endoscopic and histological surveillance based on the OLGA stage at enrollment. Stricter follow-up may be warranted for at-risk endoscopic lesions, as well as for clinical variables such as age, sex, family history of gastric cancer, and biological risk factors such as a predominance of incomplete-type IM.[16]

These findings from long-term EGD/histology follow-up suggest:

- Irrespective of the histological stage at enrollment, *H. pylori*-positive status requires treating for infection.[2,75]

- In low-risk OLGA stages, evidence of widespread mucosal intestinalization on EGD,[16] as well as the open-type Takemoto's atrophy patterns,[76] or any focal lesions (as detected by "conventional" white-light or by any other more sophisticated optical imaging technologies) requires extending the diagnostic workup.[77,78]

- In patients with OLGA stage II (antral atrophy: G=0; oxyntic atrophy: G2 [i.e., oxyntic-restricted atrophy and inflammation]), the etiopathogenetic hypothesis of AIG can be plausibly suggested.[43] This hypothesis can be further substantiated by the concomitant observation of ECL hyperplasia. Such a gastritis phenotype should prompt the following actions: 1) including the histology-based etiological hypothesis in the his-

tology report; 2) recommending serological testing for gastric (and extra-gastric) autoimmunity, hematological disorders (such as pernicious anemia); 3) suggesting endoscopic duodenoscopy (EGD) or histology surveillance that encompasses both the disease-specific risk of Type I neuroendocrine tumors and the infrequent occurrence of epithelial precancer or cancer lesions; and 4) investigating AIG-associated comorbidities, particularly inflammatory and neoplastic thyroid conditions.[43]

THE SEROLOGICAL COUNTERPART OF GASTRIC MUCOSA ATROPHY

For at least three decades, "functional" gastric serology (i.e., Pg-1, Pg-2, Pg-1:Pg-2, and gastrin) has been proposed as a non-invasive and inexpensive method to identify subjects at increased risk for GC. Large-scale epidemiological studies have shown a strong correlation between mucosal atrophy and the pepsinogen ratio. Based on this evidence, Pg-serology has been proposed as a screening tool for patients who require further invasive diagnostic procedures.[79-81] However, beyond epidemiology, the clinical reliability of serology for ranking the severity of atrophy in individual patients remains controversial.

The limited use of serology in diagnostic practice is affected by significant biases, including demographic and lifestyle variables, local *H. pylori* epidemiology, current or prior *H. pylori* status, and ongoing therapies.[82-85] To minimize the confounding effect of these variables, the patient's specific serology could be tested along with histology at index endoscopy. This serology could serve as a reference for a multimodal approach to atrophy monitoring that may replace non-invasive and invasive (more expensive EGD with biopsy) surveillance.[86,87]

CONCLUSIONS

In Western countries, fewer than 30% of patients with GC survive for more than 3 years after diagnosis. This unacceptable mortality rate is due to neoplastic dissemination that has already occurred by the time GC is detected.[88]

A global analysis by the International Agency for Research on Cancer (IARC) has recently reported that up to four in ten cancer cases worldwide (approximately 7.1 million cases) could be prevented. Gastric malignancies rank second among the most prevalent cancers worldwide,[89] accounting for nearly half of all preventable cancers in both sexes. *H. pylori* eradication programs and cancer screening strategies have demonstrated efficacy in East Asian epidemiological settings, particularly in Korea and Japan. These initiatives have achieved significant success and anticipate even more promising outcomes.[90-95]

To gain insights from the Asian model, the GC secondary prevention task force should include healthcare decision makers, general practitioners, gastroenterologists, endoscopists, and pathologists.[17,96,97] In this collaborative effort, pathologists are required to generate diagnostic messages that assess personalized GC risk, thereby providing reliable information for tailoring surveillance protocols.[2,16,98]

Authors' Contribution

Conceptualization: Massimo Rugge. Data curation: Giulia Fiorini, Marta Sbaraglia. Methodology: Massimo Rugge, Robert M Genta, Gavino Faa. Writing—original draft: Massimo Rugge. Writin—review & editing: Massimo Rugge, Robert M Genta. Approval of final manuscript: all authors.

ORCID iDs

Massimo Rugge https://orcid.org/0000-0002-0679-0563
Marta Sbaraglia https://orcid.org/0000-0002-7116-6513
Giulia Fiorini https://orcid.org/0000-0003-0381-8302
Gavino Faa https://orcid.org/0000-0002-0189-8612
Robert M Genta https://orcid.org/0000-0002-3678-7023

REFERENCES

1. Hunt RH, Camilleri M, Crowe SE, et al. The stomach in health and disease. Gut 2015;64:1650-1668.
2. Malfertheiner P, Megraud F, Rokkas T, et al. Management of *Helicobacter pylori* infection: the maastricht VI/florence consensus report. Gut 2022;71:1724-1762.
3. Di Mario F, Crafa P, Barchi A, et al. Pepsinogen II in gastritis and *Helicobacter pylori* infection. Helicobacter 2022;27:e12872.
4. Lee SY. Endoscopic gastritis, serum pepsinogen assay, and *Helicobacter pylori* infection. Korean J Intern Med 2016;31:835-844.
5. Zagari RM, Rabitti S, Greenwood DC, Eusebi LH, Vestito A, Bazzoli F. Systematic review with meta-analysis: diagnostic performance of the combination of pepsinogen, gastrin-17 and anti-*Helicobacter pylori* antibodies serum assays for the diagnosis of atrophic gastritis. Aliment Pharmacol Ther 2017;46:657-667.
6. Graham DY. Letter: questions regarding the diagnostic performance of serum assays for atrophic gastritis. Aliment Pharmacol Ther 2017; 46:1117-1118.
7. Bang CS, Lee JJ, Baik GH. Prediction of chronic atrophic gastritis and gastric neoplasms by serum pepsinogen assay: a systematic review and meta-analysis of diagnostic test accuracy. J Clin Med 2019;8:657.
8. Chapelle N, Petryszyn P, Blin J, et al. A panel of stomach-specific biomarkers (GastroPanel®) for the diagnosis of atrophic gastritis: a prospective, multicenter study in a low gastric cancer incidence area. Helicobacter 2020;25:e12727.
9. Chen MJ, Fang YJ, Chen CC, et al. Overall and stratified accuracies of *H. pylori* serology testing: a multicenter study of 8497 screening-naïve adults. Helicobacter 2025;30:e70074.
10. Rugge M, Fassan M, Pizzi M, et al. Autoimmune gastritis: histology phenotype and OLGA staging. Aliment Pharmacol Ther 2012;35: 1460-1466.
11. Bakulina N, Tikhonov S, Malkov V, et al. Non-invasive screening of autoimmune atrophic gastritis in asymptomatic subjects by serological biomarker test (GastroPanel®). Anticancer Res 2022;42:1517-1526.
12. Rugge M, Genta RM, Malfertheiner P, et al. RE.GA.IN.: the real-world gastritis initiative-updating the updates. Gut 2024;73:407-441.
13. Osmola M, Hémont C, Romańczyk M, et al. A comparative study of different assays for autoantibodies detection in patients with autoimmune gastritis. J Transl Autoimmun 2025;10:100294.
14. Vavallo M, Butt J, Cingolani S, et al. *Helicobacter pylori* multiplex serology in patients with autoimmune atrophic gastritis negative for

Helicobacter pylori at histology: a case-control study. Dig Liver Dis 2026;58:212-219.
15. Sánchez-López JY, Díaz-Herrera LC, Rizo-de la Torre LDC. Pepsinogen I, pepsinogen II, gastrin-17, and *Helicobacter pylori* serological biomarkers in the diagnosis of precursor lesions of gastric cancer. Arch Med Sci 2024;20:1016-1021.
16. Dinis-Ribeiro M, Libânio D, Uchima H, et al. Management of epithelial precancerous conditions and early neoplasia of the stomach (MAPS III): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG) and European Society of Pathology (ESP) Guideline update 2025. Endoscopy 2025;57:504-554.
17. Luzko I, Moreira L, Bornschein J. Screening for and surveillance of premalignant conditions of the stomach. Best Pract Res Clin Gastroenterol 2025;75:101978.
18. Sugano K, Tack J, Kuipers EJ, et al. Kyoto global consensus report on *Helicobacter pylori* gastritis. Gut 2015;64:1353-1367.
19. World Health Organization. Communicable and noncommunicable diseases, and mental health [Internet]. [accessed on March 20, 2026]. Available from: https://www.who.int/our-work/communicable-and-noncommunicable-diseases-and-mental-health.
20. Graham DY. *Helicobacter pylori.* In: Bagnoli F, Del Giudice G, Phogat SK, Rappuoli R, eds. Human challenge studies for vaccine development. Current topics in microbiology and immunology. vol 445. Cham: Springer, Cham, 2021:127-154.
21. Rugge M, Correa P, Di Mario F, et al. OLGA staging for gastritis: a tutorial. Dig Liver Dis 2008;40:650-658.
22. Rugge M, Pennelli G, Pilozzi E, et al. Gastritis: the histology report. Dig Liver Dis 2011;43(Suppl 4):S373-S384.
23. Massironi S. Autoimmune gastritis: an organ-specific disease or a model of systemic autoimmunity? Parallels, divergences, and emerging insights. Expert Rev Gastroenterol Hepatol 2025;19:1209-1217.
24. Massironi S, Zilli A, Elvevi A, Invernizzi P. The changing face of chronic autoimmune atrophic gastritis: an updated comprehensive perspective. Autoimmun Rev 2019;18:215-222.
25. Correa P, Haenszel W, Tannenbaum S. Epidemiology of gastric carcinoma: review and future prospects. Natl Cancer Inst Monogr 1982; 62:129-134.
26. Pizzi M, Saraggi D, Fassan M, Megraud F, Di Mario F, Rugge M. Secondary prevention of epidemic gastric cancer in the model of *Helicobacter pylori*-associated gastritis. Dig Dis 2014;32:265-274.
27. Rugge M, Correa P, Dixon MF, et al. Gastric mucosal atrophy: interobserver consistency using new criteria for classification and grading. Aliment Pharmacol Ther 2002;16:1249-1259.
28. Halimi A, Msherghi A, Nounou MV, et al. Accuracy of AI-based raman spectroscopy in the diagnosis of gastric cancer: a systematic review and meta-analysis. Lasers Med Sci 2026;41:8.
29. Kriukova E, Mazurenka M, Marcazzan S, et al. Probing field cancerization in the gastrointestinal tract using a hybrid Raman and partial wave spectroscopy microscope. Anal Chem 2025;97:12642-12653.
30. Curtius K, Wright NA, Graham TA. An evolutionary perspective on field cancerization. Nat Rev Cancer 2018;18:19-32.
31. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology 1994;19:1513-1520.
32. Capelle LG, de Vries AC, Haringsma J, et al. 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.
33. Rugge M, de Boni M, Pennelli G, et al. Gastritis OLGA-staging and gastric cancer risk: a twelve-year clinico-pathological follow-up study. Aliment Pharmacol Ther 2010;31:1104-1111.
34. Rugge M, Genta RM; OLGA Group. Staging gastritis: an international proposal. Gastroenterology 2005;129:1807-1808.
35. Ruiz B, Garay J, Johnson W, et al. Morphometric assessment of gastric antral atrophy: comparison with visual evaluation. Histopathology 2001;39:235-242.
36. Goldenring JR. Pyloric metaplasia, pseudopyloric metaplasia, ulcer-associated cell lineage and spasmolytic polypeptide-expressing metaplasia: reparative lineages in the gastrointestinal mucosa. J Pathol 2018;245:132-137.
37. Nam KT, O'Neal RL, Coffey RJ, Finke PE, Barker N, Goldenring JR. Spasmolytic polypeptide-expressing metaplasia (SPEM) in the gastric oxyntic mucosa does not arise from Lgr5-expressing cells. Gut 2012; 61:1678-1685.
38. Shimizu T, Choi E, Petersen CP, et al. Characterization of progressive metaplasia in the gastric corpus mucosa of Mongolian gerbils infected with *Helicobacter pylori*. J Pathol 2016;239:399-410.
39. Rugge M, Sacchi D, Genta RM, et al. Histological assessment of gastric pseudopyloric metaplasia: intra- and inter-observer consistency. Dig Liver Dis 2021;53:61-65.
40. Zhang T, Hu L, Zhang B, Tang X. Spasmolytic polypeptide-expressing metaplasia (SPEM): the hidden linchpin in gastric carcinogenesis beyond the correa cascade. Int J Surg 2026;112:7951-8035.
41. Yoshizawa N, Takenaka Y, Yamaguchi H, et al. Emergence of spasmolytic polypeptide-expressing metaplasia in Mongolian gerbils infected with *Helicobacter pylori*. Lab Invest 2007;87:1265-1276.
42. Binder V, Söltoft J, Gudmand-Höyer E. Histological and histochemical changes in the jejunal mucosa in ulcerative colitis. Scand J Gastroenterol 1974;9:293-297.
43. Rugge M, Bricca L, Guzzinati S, et al. Autoimmune gastritis: long-term natural history in naïve *Helicobacter pylori*-negative patients. Gut 2023;72:30-38.
44. Goldenring JR. Spasmolytic polypeptide-expressing metaplasia (SPEM) cell lineages can be an origin of gastric cancer. J Pathol 2023; 260:109-111.
45. Goldenring JR, Nam KT, Wang TC, Mills JC, Wright NA. Spasmolytic polypeptide-expressing metaplasia and intestinal metaplasia: time for reevaluation of metaplasias and the origins of gastric cancer. Gastroenterology 2010;138:2207-2210.e1.
46. Graham DY, Rugge M, Genta RM. Diagnosis: gastric intestinal metaplasia - what to do next? Curr Opin Gastroenterol 2019;35:535-543.
47. Genta RM, Turner KO, Robiou C, Singhal A, Rugge M. Incomplete intestinal metaplasia is rare in autoimmune gastritis. Dig Dis 2023; 41:369-376.
48. Driva TS, Sakellariou S, Theochari I, Gadetsakis G, Koutsoumpas A, Delladetsima I. New insights in metaplasia in autoimmune gastritis. Histopathology 2026;88:1051-1058.
49. Cassaro M, Rugge M, Gutierrez O, Leandro G, Graham DY, Genta RM. Topographic patterns of intestinal metaplasia and gastric cancer. Am J Gastroenterol 2000;95:1431-1438.
50. Rugge M. Gastric cancer risk in patients with *Helicobacter pylori* infection and following its eradication. Gastroenterol Clin North Am 2015;44:609-624.
51. Rugge M, de Boni M, Pennelli G, Mescoli C, Graham DY. OLGA can guard the barn. Am J Gastroenterol 2009;104:3099.
52. Pelizzaro F, Cardin R, Maddalo G, et al. Differential target of oxidative damage in *Helicobacter pylori*-related and autoimmune atrophic gastritis: a single-center study. Front Med (Lausanne) 2025;12:1583833.
53. Vavallo M, Cingolani S, Cozza G, et al. Autoimmune gastritis and hypochlorhydria: known concepts from a new perspective. Int J Mol Sci 2024;25:6818.
54. de Vries AC, Kuipers EJ, Rauws EA. *Helicobacter pylori* eradication and gastric cancer: when is the horse out of the barn? Am J Gastroenterol 2009;104:1342-1345.
55. Rugge M, Savarino E, Sbaraglia M, Bricca L, Malfertheiner P. Gastritis: the clinico-pathological spectrum. Dig Liver Dis 2021;53:1237-1246.
56. Kimura K. Chronological transition of the fundic-pyloric border determined by stepwise biopsy of the lesser and greater curvatures of the stomach. Gastroenterology 1972;63:584-592.
57. Rugge M, Di Mario F, Cassaro M, et al. Pathology of the gastric antrum and body associated with *Helicobacter pylori* infection in non-

ulcerous patients: is the bacterium a promoter of intestinal metaplasia? Histopathology 1993;22:9-15.
58. Lenti MV, Rugge M, Lahner E, et al. Autoimmune gastritis. Nat Rev Dis Primers 2020;6:56.
59. den Hollander WJ, Holster IL, den Hoed CM, et al. Surveillance of premalignant gastric lesions: a multicentre prospective cohort study from low incidence regions. Gut 2019;68:585-593.
60. Isajevs S, Savcenko S, Liepniece-Karele I, et al. High-risk individuals for gastric cancer would be missed for surveillance without subtyping of intestinal metaplasia. Virchows Arch 2021;479:679-686.
61. 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.e7.
62. Yue H, Shan L, Bin L. The significance of OLGA and OLGIM staging systems in the risk assessment of gastric cancer: a systematic review and meta-analysis. Gastric Cancer 2018;21:579-587.
63. Delgado Guillena PG, Cuatrecasas M, Montori S, et al. The OLGIMA system for gastric cancer risk assessment. A useful method based on the histological Sydney consensus. Histopathology 2026;88:911-921.
64. Dixon MF, Genta RM, Yardley JH, Correa P. Classification and grading of gastritis. The updated Sydney System. International Workshop on the Histopathology of Gastritis, Houston 1994. Am J Surg Pathol 1996;20:1161-1181.
65. de Vet HC, Koudstaal J, Kwee WS, Willebrand D, Arends JW. Efforts to improve interobserver agreement in histopathological grading. J Clin Epidemiol 1995;48:869-873.
66. Rugge M, Fassan M, Pizzi M, et al. Operative link for gastritis assessment vs operative link on intestinal metaplasia assessment. World J Gastroenterol 2011;17:4596-4601.
67. Isajevs S, Liepniece-Karele I, Janciauskas D, et al. Gastritis staging: interobserver agreement by applying OLGA and OLGIM systems. Virchows Arch 2014;464:403-407.
68. Matysiak-Budnik T, Camargo MC, Piazuelo MB, Leja M. Recent guidelines on the management of patients with gastric atrophy: common points and controversies. Dig Dis Sci 2020;65:1899-1903.
69. Nieminen AA, Kontto J, Puolakkainen P, Virtamo J, Kokkola A. Comparison of operative link for gastritis assessment, operative link on gastric intestinal metaplasia assessment, and TAIM stagings among men with atrophic gastritis. World J Gastroenterol 2020;26:3447-3457.
70. Riquelme A, Silva F, Reyes D, Latorre G. Chronic atrophic gastritis and intestinal metaplasia: a Latin American perspective. Korean J Helicobacter Up Gastrointest Res 2024;24:218-230.
71. Na YS, Kim SG, Cho SJ. Risk assessment of metachronous gastric cancer development using OLGA and OLGIM systems after endoscopic submucosal dissection for early gastric cancer: a long-term follow-up study. Gastric Cancer 2023;26:298-306.
72. Rugge M, Genta RM, Fassan M, et al. OLGA gastritis staging for the prediction of gastric cancer risk: a long-term follow-up study of 7436 patients. Am J Gastroenterol 2018;113:1621-1628.
73. Rugge M, Meggio A, Pravadelli C, et al. Gastritis staging in the endoscopic follow-up for the secondary prevention of gastric cancer: a 5-year prospective study of 1755 patients. Gut 2019;68:11-17.
74. Latorre G, Espino A, Araya R, et al. Chilean association of digestive endoscopy (ACHED) guidelines for the detection of early gastric cancer and surveillance of gastric premalignant conditions in high-risk populations. Gastroenterol Hepatol 2026;49:502633.
75. Yang H, Mou Y, Hu B. Discussion on the common controversies of *Helicobacter pylori* infection. Helicobacter 2023;28:e12938.
76. Zhang Y, Feng Y, You C, Zhang L. Relationship between *Helicobacter pylori* infection and different pathological types of chronic atrophic gastritis and analysis of serum gastric function. J Infect Dev Ctries 2025;19:1774-1779.
77. Rugge M, Cassaro M, Di Mario F, et al. The long term outcome of gastric non-invasive neoplasia. Gut 2003;52:1111-1116.
78. Rugge M, Leandro G, Farinati F, et al. Gastric epithelial dysplasia. How clinicopathologic background relates to management. Cancer 1995;76:376-382.
79. Chae H, Lee JH, Lim J, et al. [Clinical utility of serum pepsinogen levels as a screening test of atrophic gastritis]. Korean J Lab Med 2008;28:201–206. Korean
80. Huang YK, Yu JC, Kang WM, et al. Significance of serum pepsinogens as a biomarker for gastric cancer and atrophic gastritis screening: a systematic review and meta-analysis. PLoS One 2015;10:e0142080.
81. Zhou MJ, Huang RJ. Catching up with the world: pepsinogen screening for gastric cancer in the United States. Cancer Epidemiol Biomarkers Prev 2022;31:1257-1258.
82. Jiaojiao H, Jiaying Y, Yuling T. Regional variations in serum pepsinogen levels and their influencing factors: a multi-center cross-sectional study. Sci Rep 2026;16:7773.
83. Ang TL, Fock KM, Dhamodaran S, Teo EK, Tan J. Racial differences in *Helicobacter pylori*, serum pepsinogen and gastric cancer incidence in an urban Asian population. J Gastroenterol Hepatol 2005;20:1603-1609.
84. Zhang T, Meng X, Wang X, et al. Associations of serum pepsinogen and Gastrin-17 with *Helicobacter pylori* infection, sex, and age, in an asymptomatic coastal population: a cross-sectional study in Rizhao, China. PLoS One 2025;20:e0335228.
85. Razuka-Ebela D, Polaka I, Daugule I, et al. Factors associated with false negative results in serum pepsinogen testing for precancerous gastric lesions in a European population in the GISTAR study. Diagnostics (Basel) 2022;12:1166.
86. Bornschein J, Selgrad M, Wex T, Kuester D, Malfertheiner P. Serological assessment of gastric mucosal atrophy in gastric cancer. BMC Gastroenterol 2012;12:10.
87. Kotelevets SM, Chekh SA, Chukov SZ. Effectiveness of serological markers of gastric mucosal atrophy in the gastric precancer screening and in cancer prevention. World J Gastrointest Endosc 2024;16:462-471.
88. Rugge M, Genta RM, Graham DY, et al. Chronicles of a cancer foretold: 35 years of gastric cancer risk assessment. Gut 2016;65:721-725.
89. World Health Organization. Four in ten cancer cases could be prevented globally [Internet]. [accessed on March 20, 2026]. Available from: https://www.who.int/news/item/03-02-2026-four-in-ten-cancer-cases-could-be-prevented-globally.
90. Kim IH, Kang SJ, Choi W, et al. Korean practice guidelines for gastric cancer 2024: an evidence-based, multidisciplinary approach (update of 2022 guideline). J Gastric Cancer 2025;25:5-114.
91. Liou JM, Malfertheiner P, Lee YC, et al. Screening and eradication of *Helicobacter pylori* for gastric cancer prevention: the Taipei global consensus. Gut 2020;69:2093-2112.
92. Luu XQ, Lee K, Jun JK, Suh M, Choi KS. Socioeconomic inequality in organized and opportunistic screening for gastric cancer: results from the Korean National Cancer Screening Survey 2009-2022. Front Public Health 2023;11:1256525.
93. 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.
94. Luu XQ, Lee K, Jun JK, Suh M, Jung KW, Choi KS. Effect of gastric cancer screening on long-term survival of gastric cancer patients: results of Korean national cancer screening program. J Gastroenterol 2022;57:464-475.
95. Park JY, Kim MS, Kim BJ, Kim JG. A 6-year nationwide population-based study on the current status of gastric endoscopic resection in Korea using administrative data. Sci Rep 2023;13:7203.
96. Marcos P, Gonçalves N, Gama J, Areia M, Dinis-Ribeiro M. Standardizing endoscopic protocols increases detection of gastric cancer during surveillance of patients with precancerous conditions: a systematic review and meta-analysis. Dig Liver Dis 2025;57:1588-1602.
97. Nagula S, Parasa S, Laine L, Shah SC. AGA clinical practice update on high-quality upper endoscopy: expert review. Clin Gastroenterol Hepatol 2024;22:933-943.
98. Rugge M, Genta RM, Di Mario F, et al. Gastric cancer as preventable disease. Clin Gastroenterol Hepatol 2017;15:1833-1843.