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Improving the Endoscopic Detection and Management of Gastric Intestinal Metaplasia Through Training: A Practical Guide

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Gastric intestinal metaplasia (GIM) is a premalignant condition of the stomach characterized by the replacement of the normal gastric mucosa by intestinal epithelium in response to chronic gastric inflammation. Chronic infection with *Helicobacter pylori* is the most common trigger for GIM, but other etiologies are recognized, including autoimmune gastritis. GIM is associated with a baseline 0.16% annual risk of gastric adenocarcinoma.[1] However, the baseline risk of gastric cancer (GC) among patients with GIM may be significantly higher depending on the anatomic extent of GIM in the stomach, stage and severity of GIM, histological subtype of GIM, and the presence of *H pylori* infection, among other factors.

Improved detection, risk stratification, and management of GIM represents a major opportunity for GC prevention and early detection. Unfortunately, little if any training on GIM detection and management occurs during standard GI fellowship, especially in the United States, which is in direct contrast to the attention focused on other precancerous gastrointestinal (GI) conditions, namely, colorectal adenomas and Barrett's esophagus. Hand in hand with training in fellowship, GI proceduralists at large should also have focused training given the low baseline awareness of GIM management and highly variable practice patterns observed, even among providers routinely caring for populations at high risk for GC.[2,3] The primary objective of this article is to provide an overview of the essential elements of GIM detection, risk stratification, and management that should be incorporated into training and clinical practice.

Understand Who Is at Risk

It goes without saying that we should be performing a high-quality upper endoscopy for every patient, but it is helpful to have a pretest probability for gastric (pre) neoplasia before the endoscopic examination (Figure 1*A*). This process is analogous to performing high-quality colonoscopies for everyone, but having a heightened sense in someone presenting for colonoscopy for the evaluation of a positive Cologuard test. Based on data from Western populations, GIM is observed in approximately 5%–15% of patients undergoing upper endoscopy with gastric biopsies.[4,5] However, the prevalence is significantly higher in certain populations, including non-White groups and first-generation immigrants from countries where *H pylori* and GC are endemic, approaching or exceeding 40%, particularly in those who are older and with additional risk factors.[5–9] As expected, high-risk populations for GIM parallel high-risk populations for GC. GC is significantly more common in non-White groups compared with non-Hispanic Whites[6,10]; in fact, the rates of GC in the former greatly exceed rates of esophageal cancer and, in some (eg, Korean Americans) even approach the rates of colorectal cancer. Additional risk factors for GIM include persistent *H pylori* infection, male sex, smoking, and having a first-degree relative with GC, each conferring an independent risk of GIM ranging from approximately 1.5- to 3.5-fold.[1,5,9,11]

Know What You Are Looking For: Endoscopic Features of GIM

Endoscopic detection of GIM is not a routine focus of GI training in the United States, despite its prevalence and designation as a precancerous condition. GIM has different endoscopic features depending on the type of image enhancement (eg, narrow band imaging [NBI], linked color imaging, blue laser imaging). The most routinely available technology in the United States is high-definition white light endoscopy (HD-WLE) and NBI. Under HD-WLE, GIM often appears as subtle nodularity with ridged or tubulovillous mucosal pattern, which is more readily appreciated using NBI (Figure 1*B–G*). GIM can be appreciated even without magnifying endoscopy, which is not routinely available in the United States, although newer endoscopes in the United States have near-focus capability, which similarly enhances mucosal features (Figure 1*D–G*). One large prospective

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Pre-Endoscopy

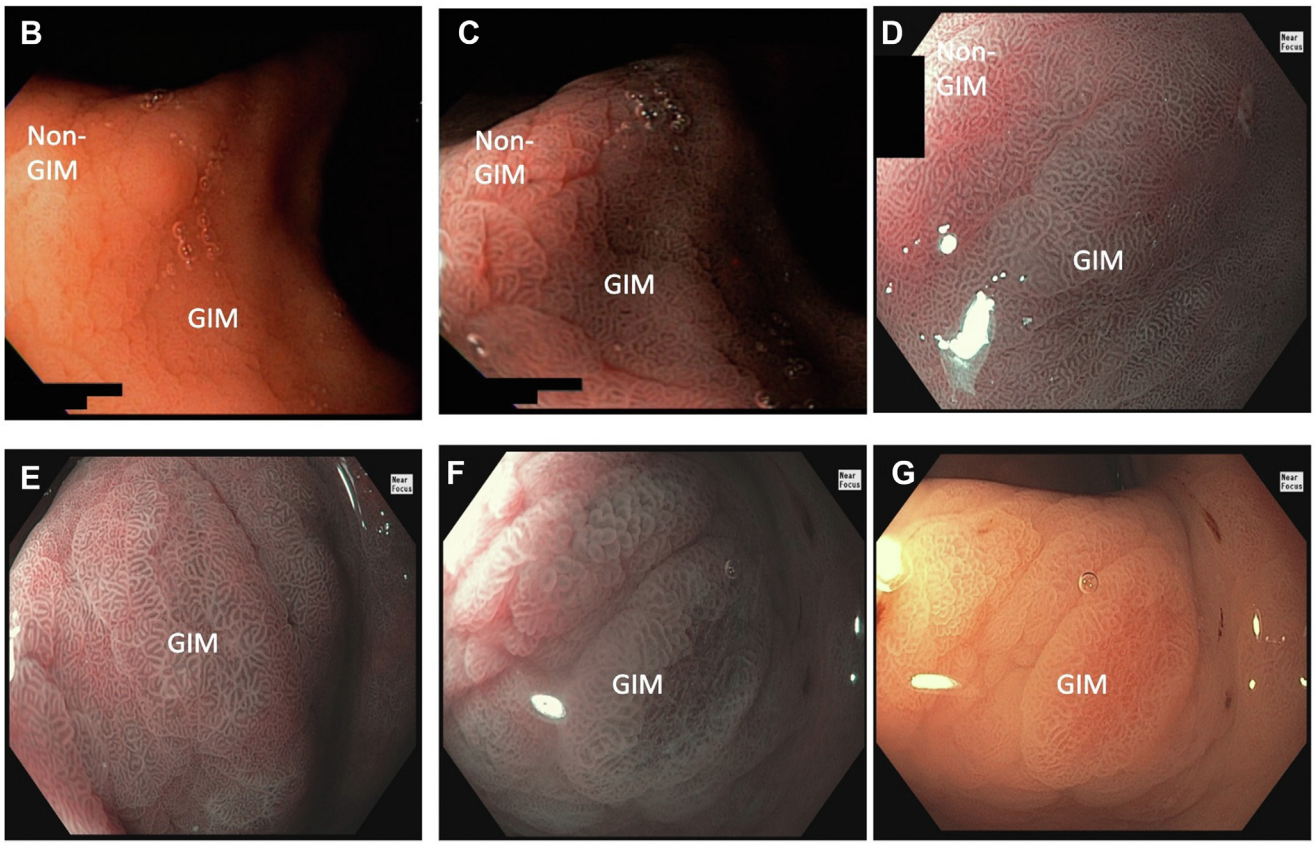
- **Recognize who is at risk** (demographics incl. age, sex, race, ethnicity, birth country; *H. pylori* infection; lifestyle factors incl diet, smoking; family history)
- **Recognize endoscopic features of gastric (pre)neoplasia**

High-quality Endoscopy

- **Ensure appropriate equipment** (HD-WLE + NBI, at minimum)
- **Achieve excellent mucosal visualization** (mucosal cleansing, adequate insufflation)
- **Ensure adequate gastric inspection time** (~6-7 minutes at least)
- **Ensure adequate description of findings and photo-documentation**
- **Ensure appropriate biopsies are obtained and placed in separately labelled jars** (Sydney protocol biopsies +/- any concerning lesions)

Post-endoscopy

- **Histological confirmation of GIM**
- **Risk stratification** (Histological severity/stage, histological subtype, demographic, lifestyle, and clinical factors)
- **Treat *H. pylori* infection if present and confirm successful eradication**
- **Apply a risk-based approach to determine whether endoscopic surveillance is indicated and at what interval, and ensure this is consistent with the patient's wishes**



multicenter study demonstrated that the respective sensitivity and specificity of HD-WLE with NBI (without magnification) was 87% and 97% for GIM, and 92% and 99% for dysplasia.[12] Other characteristic features of GIM that can be appreciated with NBI include the light blue crest sign (Figure 1*D*, *E*), which has a high sensitivity and specificity (≥90%) for GIM and the presence of white opaque fields,"[13] which is also appreciated using HD-WLE and has very high specificity, but limited sensitivity. Recognizing the endoscopic features of atrophic gastritis is also relevant, because GIM almost invariably implies a background of atrophic gastritis.[13]

Endoscopic features of gastric neoplasia are beyond the scope of this article, but it cannot be emphasized enough that gastric neoplastic lesions are often very subtle, especially in patients who are *H pylori* negative. Even in expert hands, endoscopic miss rates are approximately 10%, with several series reporting rates as high as 20%–25%.[14] The core metrics of mucosal visualization and inspection time are associated with improved detection rates (discussed elsewhere in this article) (Figure 1*A*). Creating online resources such as photo and video libraries and interactive learning modules may help to train endoscopists to recognize the endoscopic features of gastric (pre)neoplasia, especially in low- to intermediate-risk countries such as the United States, where such resources do not currently exist.

Set Yourself up for Success: Performing a High-quality Upper Endoscopy

GIM and gastric neoplasia are subtle. Achieving excellent gastric mucosal visualization through cleansing and insufflation and spending sufficient time carefully inspecting all aspects of the gastric mucosa ensuring no areas are missed are critical to the endoscopic detection of (pre)neoplasia (Figure 1*A*); indeed, these concepts parallel the impact of colonic bowel preparation quality and withdrawal time on adenoma detection rates. Water irrigation alone is often insufficient, and defoaming and mucolytic agents (eg, simethicone) may be needed.[13] Adequate insufflation allows a broad survey of the entire gastric mucosa for abnormalities. Subtle features that might suggest gastric neoplasia include incomplete distensibility of gastric folds or disruption or abnormal convergence of folds. The optimal gastric inspection time for neoplasia detection has not been established, but ≥6–7 minutes measured from the time of adequate mucosal visualization is a proposed threshold.[15–17]

The endoscopic examination should be performed with HD-WLE at a minimum. Image-enhancing technology, such as NBI, has been consistently demonstrated to improve detection of GIM compared with HD-WLE alone. There have been many advances in endoscopic technologies to improve the detection of GIM, and, more important, gastric neoplasia (eg, image-enhancement with linked color imaging). Notwithstanding important considerations and relevant limitations, which are beyond the scope of this article, training in advanced endoscopic technology, including artificial intelligence, will ideally be incorporated into training programs with as much enthusiasm in the stomach as for other parts of the GI tract. Regardless, training efforts should at least focus on ensuring that the basic metrics of gastric mucosal visualization, inspection time, and photodocumentation of landmarks are routinely achieved and monitored.

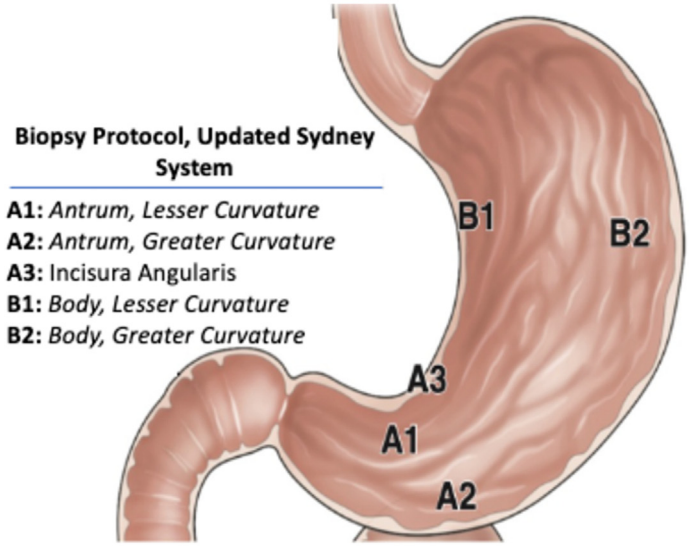
Understand Risk Stratification Factors for Patients With GIM

In the United States, a diagnosis of GIM necessitates histopathological confirmation and, therefore, biopsies are required (Figure 2*A*). Obtaining appropriate biopsies is also a pillar for risk stratification, because this process allows for the determination and confirmation of the (1) anatomic extent, (2) histopathological stage and severity, (3) histological subtype (incomplete vs complete vs mixed), and (4) presence of *H pylori* (although it should be noted that the sensitivity for *H pylori* diagnosis is lower in the presence of GIM, and other nonserological modalities, such as fecal antigen testing, should be considered). These factors alone may be associated with a significant 2-to 20-fold (eg, OLGIM III/IV) higher risk of incident advanced gastric neoplasia and are critical to determining whether or not patients warrant endoscopic surveillance and, if so, at what interval.[1,18]

In patients with established or suspected GIM or who are at elevated risk, biopsies according to the updated Sydney protocol should be obtained (Figure 2*A*) and should be targeted to areas concerning for GIM. One should ensure that the incisura angularis is biopsied since GIM often involves this area and it is needed for histological risk stratification using the Operative Link for Gastritis (OLGA) and Gastric Intestinal Metaplasia (OLGIM) Assessment (described elsewhere in this article) (Figure 2*B*).[19,20] Any concerning lesions should be photodocumented with their location clearly described in the procedure report, biopsied, and placed in a separately labeled jar. The data obtained from the preprocedure assessment supplements the histological risk assessment. Older age, family history of GC in a first-degree relative, tobacco smoking, and certain dietary factors (eg, diets high in salt or smoked/preserved meats and low in fresh produce) are also associated with increased risk of GC among patients with

Figure 1. (*A*) Flow diagram illustrating the optimal pre-endoscopy, intraendoscopy, and postendoscopy steps that should be incorporated into gastroenterological training to improve gastric intestinal metaplasia (GIM) detection and management. (*B*–*G*) Endoscopic appearance of GIM located at the incisura angularis. (*B* and *G*) Characteristic endoscopic features of GIM under high-definition white light endoscopy, including subtle nodularity and tubulovillous pattern of the surface mucosa, which is better appreciated on narrow band imaging (NBI). (*B*–*F*) NBI also highlights the light blue crest sign that is characteristic of GIM. (*D*, *E*) Near-focus endoscopy enhances these mucosal features (*D*–*G*). (Some images courtesy of Dr Gonzalo Latorre, Pontificia Universidad Católica de Chile, Santiago, Chile; and Dr Dan Li, Kaiser Permanente, Santa Clara, CA.)

A



B

		CORPUS Biopsies			
		Score 0 *No GIM present*	**Score 1** *Mild GIM*	**Score 2** *Moderate GIM*	**Score 3** *Severe GIM*
ANTRUM Biopsies (including Incisura)	**Score 0** *No GIM present*	Stage 0	Stage I	Stage II	Stage II
	Score 1 *Mild GIM*	Stage I	Stage I	Stage II	Stage III
	Score 2 *Moderate GIM*	Stage II	Stage II	Stage III	Stage IV
	Score 3 *Severe GIM*	Stage III	Stage III	Stage IV	Stage IV

Figure 2. (*A*, *B*) Schematic diagram of the updated Sydney protocol biopsy system and Operative Link for Gastric Intestinal Metaplasia Assessment (OLGIM) classification system. Obtaining biopsies according to the updated Sydney protocol biopsy system allows for determination of the topographic extent of gastric intestinal metaplasia (GIM) as well as the severity of GIM (and underlying atrophy), both of which are important prognostic factors for gastric cancer (GC) risk. These are incorporated in the OLGIM stage, which ranges from I (mild) to IV (severe). Compared with the Operative Link for Gastritis Assessment (OLGA), OLGIM has improved interobserver agreement but might down-stage some high-risk individuals. OLGA and OLGIM have similar prognostic value for GC, with OLGA/OLGIM III/IV being associated with a significantly higher risk of GC compared with lower OLGA/OLGIM scores. (Figure 2A adapted from Shah SC, et al. Gastroenterology 2020;158:704; and Figure 2B adapted from Capelle LG, et al. Gastrointest Endosc 2010;71:1150.)

GIM.[1] Race, ethnicity, and birth country of origin are certainly associated with higher GIM prevalence, but it is not established as to whether these factors are associated independently with progression to GC once GIM is diagnosed.[1]

Fellowship training should routinely emphasize the importance of determining and documenting each of these histological and demographic risk stratification factors, because these are currently our best measures of risk to guide recommendations surrounding surveillance intervals. Such practice is not dissimilar to using the Prague classification for nondysplastic Barrett's esophagus, and the number, size, and histology for colorectal polyps, along with clinical factors, to determine surveillance recommendations. It is fully acknowledged that surveillance recommendations are still evolving in the United States, although there is a robust body of data outside of the United States. That said, a diagnosis of GIM should not be ignored and every effort should be made to determine patients' individual risk. In addition to training and education, creating automated pathology result templates that record information on risk stratification and link to GIM surveillance reminders in patients' medical charts may decrease practice pattern variability.

Understand the Importance of Histopathology

Histopathological staging and GIM subtype are among the best GC risk predictors in our toolbox. OLGIM (and OLGA) is a validated GC risk assessment system that

incorporates both the severity and topographic distribution of GIM (and atrophy) (Figure 2*B*). OLGIM has greater interobserver reproducibility than OLGA, with similar prognostic performance for advanced gastric neoplasia.[18] Indeed, based on a recently published large, prospective, multicenter cohort of targeted endoscopic surveillance of patients residing in regions of low to intermediate GC incidence, patients with OLGIM stage III or IV had a significant 20.8-fold (95% confidence interval, 5.04–85.6) higher risk of early gastric neoplasia compared with patients without GIM (note: low-risk GIM, OLGIM stage I demonstrated no increased risk). The median time to early gastric neoplasia among patients with OLGIM stage III or IV was <2 years (22.7 months; 95% confidence interval, 12.7–44.8).[18] These patients may, therefore, warrant more aggressive surveillance, especially if there are additional risk factors. Unfortunately, histopathologic stage is not routinely reported on pathology reports among patients diagnosed with gastric preneoplasia in the United States. The reasons are multifactorial including lack of sufficient gastric sampling, since determination of OLGIM stage necessitates biopsies from the corpus, antrum, and incisura (Figure 2*B*). Buy-in from pathologists is also needed.

Reporting the histological subtype of GIM—that is, complete, incomplete, or mixed—in each gastric biopsy sample also aids in risk stratification; incomplete-type GIM is associated with a >3-fold higher risk of GC compared with the complete type and may, therefore, warrant endoscopic surveillance.[1,21] Importantly, OLGA/OLGIM stage and histological subtype are readily determined using standard hematoxylin and eosin staining and require little additional time, yet provide a wealth of information for determining whether surveillance should be recommended and at what interval.

The routine reporting of these prognosticators in pathology reports will not occur overnight and training efforts among gastroenterologists and pathologists alike are needed. One immediate step that gastroenterologists can take is to meet with their GI pathologists to discuss the evidence and rationale for GIM staging and histological subtyping, specifically citing the impact on clinical decision-making with respect to determination of surveillance intervals (including no surveillance).[1,18,21–23]

Ensure Follow-up

Training should incorporate standard processes to ensure that patients diagnosed with GIM receive appropriate follow-up. The first evidence-based United States guidelines on GIM were recently published by the American Gastroenterological Association, and generally align with international guidelines recommending a risk-stratified approach for determining whether endoscopic surveillance should be pursued. A full overview of the management of patients with GIM is beyond the scope of this article, but the core items are to ensure[23] that (1) *H pylori* is appropriately tested for, treated, and confirmed eradicated; (2) sufficient data are available for appropriate risk stratification in order to determine endoscopic surveillance vs no surveillance; (3) recommendations are discussed with patients through a shared decision-making conversation. Where applicable, additional risk modification strategies should also be discussed with patients, including smoking cessation. In the near future, there will ideally be processes in place to monitor and track how often and to what extent providers discuss follow-up recommendations with patients diagnosed with GIM, because adherence to these metrics represents an achievable opportunity to prevent or attenuate neoplastic progression in patients with GIM or at least detect gastric neoplasia at an early stage.

In conclusion, we must take active steps to incorporate GIM detection and management into training and establish quality metrics, similar to that which already occurs for other precancerous conditions of the GI tract. This strategy is particularly critical in the United States, where there is expanding diversity and enrichment for individuals at an increased risk for GC.

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