Clinical Gastroenterology and Hepatology 2023;■:■–■

CLINICAL PRACTICE: HERE AND NOW

Prasad G. Iyer, Section Editor

Management of Gastric Intestinal Metaplasia

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In the United States, approximately 26,240 new gastric cancer (GC) cases are diagnosed annually. The majority of GC diagnoses arise from the noncardia and are histologically classified as intestinal-type gastric adenocarcinoma (NCGA).[1] Gastric intestinal metaplasia (GIM) is a premalignant mucosal change that is associated with a 1.6% (range, 1.5%–1.7%) 10-year baseline risk of progression to NCGA.[2] Chronic *Helicobacter pylori* infection is the most common etiology of GIM. GIM is identifiable on careful upper endoscopy, readily characterized on histopathology with low interobserver variability, and, because of the long sojourn time from GIM to NCGA, offers an attractive opportunity for surveillance to detect NCGA at an early stage when resection is potentially curative.

The first US evidence-based guideline on GIM, which was published by the American Gastroenterological Association, distinctly highlighted the paucity of high-quality literature describing GIM epidemiology in North American populations, as well as the complete lack of direct evidence to inform whether endoscopic surveillance of GIM vs no surveillance is associated with improved GC incidence and mortality outcomes.[1] The lack of high-quality data has slowed the implementation of GIM surveillance in the United States, and led to confusion regarding how to manage GIM, particularly among populations with differential NCGA risk. The primary objective of this focused article was to review the clinical findings of GIM and the clinical management based on international guidelines

Gastric Intestinal Metaplasia Detection and Diagnosis

Pretest Probability: Individuals at Risk

It is challenging to ascertain the true population prevalence of GIM because GIM typically is asymptomatic and endoscopy with appropriate biopsies are necessary for diagnosis. Furthermore, GIM risk is not uniform across US populations. In patients undergoing endoscopy for any indication in the United States, biopsy-proven GIM prevalence is estimated to be 4.8% overall; however, GIM prevalence is reported to be significantly higher (25%–48%, or 5- to 10-fold) among high-risk groups.[3] Risk factors for GIM include non-White race, immigration from a country with a high gastric cancer incidence, male sex, tobacco use, older age, and family history of GC. Each of these risk factors should be considered before endoscopy because each of these factors is associated with significantly higher odds of GIM, ranging from 1.5- to 3.5-fold compared with the respective reference groups.[3] It goes without saying that high-quality endoscopy should be performed in all patients; however, it warrants emphasis that in patients with additional risk factors for GIM, endoscopists should ensure adequate mucosal visualization, sufficient examination time, use of high-definition white light endoscopy (HD-WLE) ideally with image enhancement, and consider Sydney protocol biopsies (see later).

Endoscopic Findings

The endoscopic appearance of atrophic gastritis, GIM, and even early stage neoplasia may be subtle and easily missed. Achieving clear mucosal visualization through cleansing and air or CO_2 insufflation, as well as ensuring adequate examination time, allows the endoscopist to sufficiently examine the appearance and architecture of the gastric mucosa, submucosal vasculature, and gastric rugae.[4] The American Gastroenterological Association suggests using a systematic approach so that all regions of gastric mucosa are examined methodically.[4] Photographic

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Abbreviations used in this paper: **GC, gastric cancer; GIM, gastric intestinal metaplasia; HD-WLE, high-definition white light endoscopy; NBI, narrow-band imaging; NCGA, noncardia gastric adenocarcinoma.**

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1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2023.03.010

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documentation of each of the major gastric stations in anterograde and retrograde view is encouraged.

On WLE examination, atrophic gastritis appears as pallorous mucosa with distinctly visible submucosal vessels and loss of gastric folds, while areas with GIM may have a nodular or ridged mucosal appearance[4] (Figure 1). Often, the light blue crest and white opaque fields signs, as well as the tubulovillous pattern, are apparent with GIM and have high specificity for the diagnosis[4] (Figure 1*A* and *B*). The light blue crest sign is named for the light blue lines on the crest of the epithelial surface and can be seen on narrow-band imaging (NBI) with or without near focus (Figure 1*A* and *B*). The white opaque fields sign is named for the white light that is scattered by the mucosal microscopic lipid droplets that accumulate in GIM and can be seen on HD-WLE.

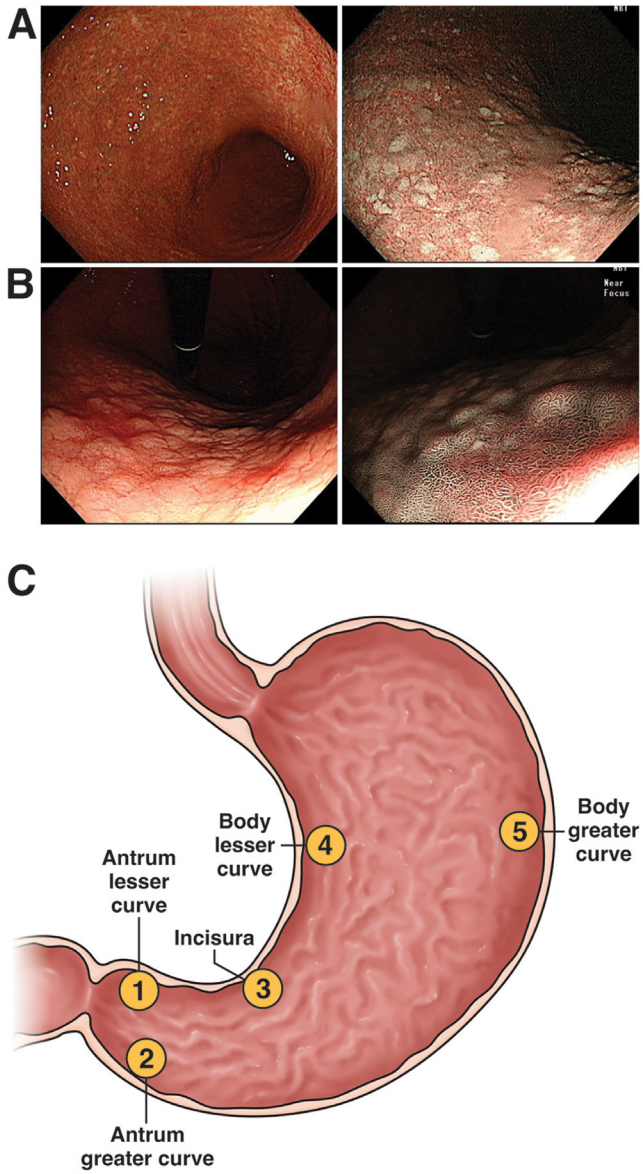

Figure 1. Endoscopic and histologic pictures of gastric intestinal metaplasia. (*A*) White light and narrow-band imaging (NBI) of gastric intestinal metaplasia, including an example of white opaque fields. (*B*) White light and NBI of gastric intestinal metaplasia, including an example of light blue crest on NBI with near focus. The mucosa is nodular and ridged and shows the classic tubulovillous pattern. (*C*) Biopsy sites for the Sydney Protocol. (*A* and *B*) Photographs courtesy of Hwoon-Yong Jung, MD, PhD.

HD-WLE is recommended over standard-definition WLE to increase the detection of gastric (pre)neoplasia. Image-enhanced endoscopy provides a more detailed discrimination of the gastric mucosal surface and blood vessels, with demonstrated higher sensitivity for GIM compared with WLE alone[4,5]; such technologies include dye-based and virtual chromoendoscopy, such as NBI. The near-focus feature of the newest-generation HD-WLE further enhances endoscopic discrimination of GIM and is readily available in the United States (Figure 1).

Role of Biopsy and Pathologic Findings

Along with a careful endoscopic examination, mapping biopsy specimens obtained according to the updated Sydney protocol are recommended to increase the diagnostic yield and allow for risk stratification.[4–6] The protocol calls for a total of 5 gastric biopsy specimens: 2 from the lesser and greater curvature of the antrum (within 2–3 cm from the pylorus), 2 from the body (1 from the lesser curvature 4 cm proximal to the incisura, and the other from the middle of the greater curvature 8 cm from the cardia), and 1 from the incisura (Figure 1*C*). One prospective US/European trial of high-risk patients compared HD-WLE alone with HD-WLE with NBI with HD-WLE ± NBI with Sydney protocol biopsy specimens and found that NBI examination with Sydney protocol biopsies identified more patients with GIM than HD-WLE alone.[6] In this study, 100% of patients with GIM were identified with the combination of HD-WLE+NBI and Sydney protocol biopsy specimens compared with 29% with HD-WLE examination alone

The updated Sydney protocol also has a high sensitivity for detection of *H pylori*.[4] In addition to defining the anatomic extent of GIM and the presence of *H pylori*, biopsy specimens also allow for describing the histologic subtype (ie, complete vs incomplete) of GIM and underlying severity of gastric atrophy and inflammation. All abnormal areas seen on endoscopy should be described in the endoscopic report and biopsied separately.[4,5] Ideally, all biopsy specimens should be placed in separately labeled jars for histopathologic analysis. This is important for determining the anatomic extent of GIM and further informs NCGA risk. If the cost per pathology jar is a concern, biopsy specimens still should be obtained from each of the Sydney protocol locations including the incisura, but they can be separated into 2 jars: antrum/incisura and body.[5]

Clinical Management of Gastric Intestinal Metaplasia

Nonendoscopic management

Once detected, there are several important factors to consider when counseling patients. All patients with GIM

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Table 1. International Recommendations on Diagnosis and Surveillance of Gastric Intestinal Metaplasia

Professional society	Recommendations
American Gastroenterological Association, Clinical Practice Guidelines on Management of Gastric Intestinal Metaplasia, 2020	Surveillance GIM does not warrant routine surveillance (very low quality evidence, conditional recommendation) Comments: Patients with GIM at higher risk for gastric cancer who put a high value on the potential but uncertain reduction in gastric cancer mortality, and who put a low value on potential risks of surveillance endoscopies, may reasonably elect for surveillance Patients with GIM specifically at higher risk of gastric cancer include those with the following: (1) incomplete vs complete GIM, (2) extensive vs limited GIM, and (3) family history of gastric cancer Patients at overall increased risk for gastric cancer include the following: (1) racial and ethnic minorities and (2) immigrants from high-incidence regions Diagnosis and staging GIM does not warrant routine repeat short-interval endoscopy with biopsies for the purpose of risk stratification (very low quality evidence, conditional; grade of recommendation) Comments: Based on shared decision making, patients with GIM and high-risk stigmata, concerns about completeness of baseline endoscopy, and/or who are at overall increased risk for gastric cancer (ie, racial and ethnic minorities, immigrants from regions with high gastric cancer incidence, or individuals with a family history of first-degree relative with gastric cancer) may reasonably elect for a repeat endoscopy within 1 year for risk stratification
British Society of Gastroenterology, 2019	Endoscopic technique Image-enhanced endoscopy techniques as opposed to white light endoscopy should be used for detection and risk stratification (moderate-quality evidence, strong recommendation) Location and extent of AG and GIM should be clearly documented with photographic evidence (low-quality evidence, strong recommendation) Diagnosis and staging If at higher risk for gastric adenocarcinoma, a full systematic examination of the stomach with clear photographic documentation of gastric regions and pathology should be performed (moderate-quality evidence, strong recommendation) If features of chronic AG are present, biopsy specimens of abnormal areas and using the Sydney protocol should be performed, and samples should be collected in separate containers (low-quality evidence, strong recommendation) Baseline screening should be considered in individuals aged $\geq$50 years with multiple risk factors for gastric adenocarcinoma (males, smokers, pernicious anemia, first-degree family history) (low-quality evidence, weak recommendation) Baseline screening should be considered in individuals aged $\geq$50 years with pernicious anemia, with biopsy specimens taken from the greater and lesser curvature (low-quality evidence, weak recommendation) Surveillance Extensive AG or GIM, defined as that affecting the antrum and body, should undergo surveillance every 3 years (low-quality evidence, strong recommendation) AG or GIM limited to the antrum would not warrant surveillance unless there is a strong family history of gastric cancer or persistent *H pylori* infection, then surveillance should be performed every 3 years (low-quality evidence, strong recommendation)

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Table 1. Continued

Professional society	Recommendations
European Society of Gastrointestinal Endoscopy, 2019	Endoscopic technique HD-CE is better than high-definition white light endoscopy alone for the detection of AG and GIM (high-quality evidence) Virtual HD-CE with or without magnification should be used when available (moderate-quality evidence, strong recommendation) Diagnosis and staging For adequate staging, a first-time examination should include gastric biopsy specimens for *H pylori* infection and for advanced stages of AG (moderate-quality evidence, strong recommendation) Biopsy specimens of at least 2 topographic sites from the antrum and body and from suspicious lesions should be taken and clearly labeled in separate vials (moderate-quality evidence, strong recommendation) Surveillance Mild to moderate AG restricted to the antrum or GIM at a single location would not warrant surveillance (moderate-quality evidence, strong recommendation) GIM at a single location with a family history of gastric cancer, or with incomplete GIM or with persistent *H pylori* gastritis should undergo surveillance every 3 years (low-quality evidence, weak recommendation) Advanced staged of AG (severe atrophic changes or GIM in both antrum and corpus) should have surveillance every 3 years (low-quality evidence, strong recommendation) Advanced staged of AG with family history of gastric cancer should have surveillance every 1–2 years (low-quality evidence, weak recommendation)
Italian Society of Gastroenterology, 2019	Endoscopic technique Whenever possible, endoscopic surveillance should be performed with high-quality endoscopy (HD-CE or virtual CE) (evidence and grade not provided) Diagnosis and staging Patients suffering from pernicious anemia, iron-deficiency anemia, or autoimmune disorders, including autoimmune thyroiditis and type 1 diabetes mellitus, should be screened (C level of evidence, grade of recommendation 1) Patients with persistent uninvestigated dyspepsia, with long-term use of proton pump inhibitors and first-degree relatives of patients with gastric cancer or chronic AG might benefit from screening (C level of evidence, grade of recommendation 2) The standard Sydney protocol with 5 biopsy specimens should be used (A level of evidence, grade of recommendation 1) Surveillance Advanced stages of AG (AG or GIM of at least moderate severity affecting both the antrum and corpus) should undergo surveillance every 3 years (C level of evidence, grade of recommendation 1) AG, when associated with pernicious anemia, should undergo surveillance every 3–5 years (B level of evidence, grade of recommendation 2)

NOTE. The presence of GIM almost invariably implies atrophic gastritis and thus there is overlap in management of these precancerous conditions.
AG, atrophic gastritis; GIM, gastric intestinal metaplasia; HD-CE, high-definition chromoendoscopy.

should be tested for active *H pylori* infection. Those with confirmed active infection should be treated with eradication therapy and undergo repeat nonserologic testing to confirm successful eradication at least 4 weeks after treatment completion. Compared with persistent infection, *H pylori* eradication is associated with a significantly reduced risk of GC, even in countries with low–intermediate GC incidence, such as the United States.[2,3,7,8] However, it is important to recognize that GIM still can progress, even in the absence of active *H pylori* infection, thus underscoring the relevance of endoscopic surveillance for neoplasia in appropriate patients (Table 1).

All patients with GIM should be counseled on relevant behavioral interventions that may reduce their risk of NCGA, such as tobacco cessation and limiting the intake of dietary salt and smoked foods.

Risk Stratification

Appropriate risk stratification is key to determining whether or not endoscopic surveillance of GIM is warranted and can inform shared decision making with the patient. Based on a comprehensive systematic review and meta-analysis, among patients with GIM, the following risk factors are associated with a higher risk of progression to NCGA: incomplete histologic subtype (vs complete), first-degree relative with GC, the presence of corpus-extended GIM (vs antral limited), persistent *H pylori* infection (vs

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negative or eradicated), and stages III to IV operating link for gastritis assessment and operating link for gastric intestinal metaplasia (vs stage 0/1).[3] Although it is well established that immigration from countries with higher NCGA incidence and non-White race are risk factors for NCGA, it is not clear that race and ethnicity alone are independent risk factors for GIM progression to NCGA.[2]

Endoscopic Surveillance of Gastric Intestinal Metaplasia

Table 1 summarizes current international guidance regarding the role of endoscopic surveillance for GIM. Unfortunately, there is a lack of direct evidence supporting the use of endoscopic surveillance of GIM for the purpose of GC early detection in the United States. Current estimates suggest a 1.6% (range, 1.5%–1.7%) 10-year cumulative incidence of gastric cancer in patients with GIM, although this baseline rate is significantly higher (anywhere from 2- to 4.5-fold) in the presence of additional risk factors described earlier. Notably, this baseline risk of progression is analogous to the risk of esophageal or colorectal adenocarcinoma in patients with nondysplastic Barrett's esophagus and low-risk adenomas, respectively, both of which are premalignant conditions routinely surveilled with endoscopy and colonoscopy.

Surveillance generally is recommended every 3 years by different gastroenterology societies internationally, depending on the presence of certain risk factors—including the anatomic extent of GIM, severity, histologic subtype, and family history, as well as shared decision making with patients (Table 1). In patients with life-limiting comorbid medical conditions and therefore limited life expectancy, surveillance may not be worthwhile given the generally long sojourn time of GIM to more advanced stages that could cause significant morbidity. The potential benefits must be weighed against even the small risk of endoscopy to inform shared decision making between patient and provider.

Take Home Message

GIM, a premalignant mucosal change, is a readily identifiable endoscopic and histologic marker of NCGA risk. By addressing modifiable risk factors such as chronic *H pylori* infection and risk stratification to select patients who might warrant endoscopic surveillance, the risk of NCGA mortality may be prevented.

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Conflicts of interest
The authors disclose no conflicts.

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