Review Article

Detection and surveillance of gastric cancer precursors: evolving guidelines and technologies

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Abstract: Non-cardiac gastric adenocarcinoma (NCGA) remains a leading source of global morbidity and mortality. Despite its lower incidence in the United States and Western Europe, the overall poor survival and prognosis from this cancer suggest a need for earlier detection. NCGA develops through a well-known stepwise progression of precursor lesions, including chronic gastritis, atrophic gastritis, intestinal metaplasia, and dysplasia. Identification and surveillance of high-risk individuals carrying these precursors may be one important avenue to improve NCGA outcomes through earlier detection. In addition, identifying NCGA precursors creates an opportunity for definitive management with early endoscopic resection, and therefore a potential for reduction in cancer morbidity and mortality. This review has two main objectives. The first aim is to describe and evaluate various imaging technologies that are currently used to aid and improve the endoscopic detection of NCGA precursor lesions. These modalities include image-enhanced endoscopy (both dye-based and virtual), confocal laser endomicroscopy, and auto-fluorescence imaging. The second aim is to appraise current surveillance strategies for individuals carrying precursor lesions, with an emphasis on synthesizing recommendations from several recent surveillance guidelines published in the United States and Europe. In this review, we also highlight future innovative technologies and directions, including the utilization of artificial intelligence for rapid lesion recognition and molecular-based individual risk stratification.

Keywords: Gastric intestinal metaplasia (GIM); atrophic gastritis; dysplasia; surveillance; endoscopy

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Introduction

Background

Gastric cancer causes significant morbidity and mortality worldwide. In 2020, there were an estimated 1 million new cases of gastric cancer and 770,000 gastric cancer deaths worldwide (1). In the United States (US), there were 26,380 estimated new cases of gastric cancer, and approximately 11,090 deaths in 2022 (2). In the US, 5-year survival is 32% across stages (2); moreover, fewer than one-third of cancers are diagnosed at a localized stage (3). As such, the majority of gastric cancers in the US are diagnosed at later stages, often with metastases, and with poor prognosis (4). Early detection of gastric cancer and pre-neoplastic lesions continues to be a challenge for clinicians.

The majority of cancers in the stomach are adenocarcinomas (90–95%). Other types of cancers which occur in the stomach include gastric lymphomas, gastrointestinal stromal tumors, and neuroendocrine tumors (5). Gastric adenocarcinomas are further divided

based on histology, as intestinal and diffuse types, and based on anatomic location, as cardia and non-cardia gastric cancers (6). This review will focus on non-cardiac gastric adenocarcinoma (NCGA), the cancer for which the etiologic role of precursor lesions is most clearly established.

Rationale and knowledge gap

Currently, there are multiple endoscopic techniques and technologies to detect and monitor gastric precursor lesions, as well as evolving surveillance guidelines from various international societies. Given the advancement in endoscopic imaging modalities and a recent trend towards early detection and management of precursors, we aim to analyze current literature and highlight overarching themes. Through this review, we discuss imaging modalities for precursor detection and risk stratification, and propose a novel management algorithm for dysplasia based on current literature.

Objective

This review was conducted to provide an overview on current endoscopic modalities to detect NCGA precursors and evaluate recently published surveillance guidelines from various societies.

Precursor lesions

The transition from normal mucosa to NCGA is believed to occur through a stepwise cascade of precursors of increasing severity, known as Correa's cascade (7). In this precancerous pathway, the normal gastric mucosa is subject to inflammation, as seen by the infiltration of polymorphonuclear neutrophils and mononuclear leukocytes on biopsy (7). Both worldwide and in the US, the leading cause of this inflammatory insult is chronic infection by *Helicobacter pylori* (Hp); it has been estimated that 89% of NCGAs were associated with Hp infection globally (8). However, in the US and other Western nations there is also a moderately high prevalence of autoimmune gastritis. Autoimmune gastritis represents an alternative pathway to carcinogenesis independent of Hp, and is characterized by reduced gastric acid secretion, elevated gastrin levels, enterochromaffin-cell hyperplasia, and in certain cases development of anti-parietal and anti-intrinsic factor antibodies (9-11). Pernicious anemia may be a late manifestation of autoimmune gastritis and may be a marker of increased cancer risk.

In both Hp-induced and autoimmune gastritis, the prolonged inflammatory state results in the loss of normal glandular structure and thinning of the mucosal layer, termed atrophic gastritis (AG) (12). The atrophy of glands can eventually be replaced by fibrosis, connective tissue, or other intestinal-type epithelial cells (7,9). The next stage is the development of gastric intestinal metaplasia (GIM), which can be pathologically recognized by the presence of goblet cells, absorptive cells, and Paneth cells (12). Histologically, GIM can be classified as either complete or incomplete. Complete GIM is characterized by small intestine-type epithelial cells with a well-defined brush border, goblet cells, and expression of small intestinal digestive enzymes. By contrast, incomplete GIM is characterized by colonic epithelium, the absence of a brush border, and loss of expression of certain digestive enzymes (7,13). It is believed that incomplete GIM has increased NCGA risk compared to complete GIM. In certain cases, GIM can advance to dysplasia, the penultimate step prior to NCGA development. Dysplasia can be broadly defined as the presence of neoplastic epithelium characterized by enlarged nuclei and cellular pleomorphism, but in the absence of invasion across the lamina propria (14). Once neoplastic cells violate the basement membrane and into the stroma, it is considered invasive carcinoma (7).

Endoscopic techniques of detection

Traditionally, white light endoscopy (WLE) has been utilized to visualize the gastric mucosa. However, there is a high degree of interobserver variability with WLE, which limits the reliability of differentiating neoplastic or pre-neoplastic gastric lesions based on conventional macroscopic visualization (15). Although there has been improvement in detection with the advent of high-definition WLE, GIM has few distinguishable macroscopic traits, which makes it particularly challenging to identify (16,17). Therefore, recent advances in technology have targeted alternative techniques to improve mucosal visualization and diagnosis of gastric lesions (18,19). In this section, we discuss the methodology and application of several advanced endoscopic imaging modalities to improve precursor detection.

Narrow-band imaging (NBI)

NBI is a method of image-enhanced endoscopy (IEE) that uses a filter to select a narrow spectrum of wavelength for

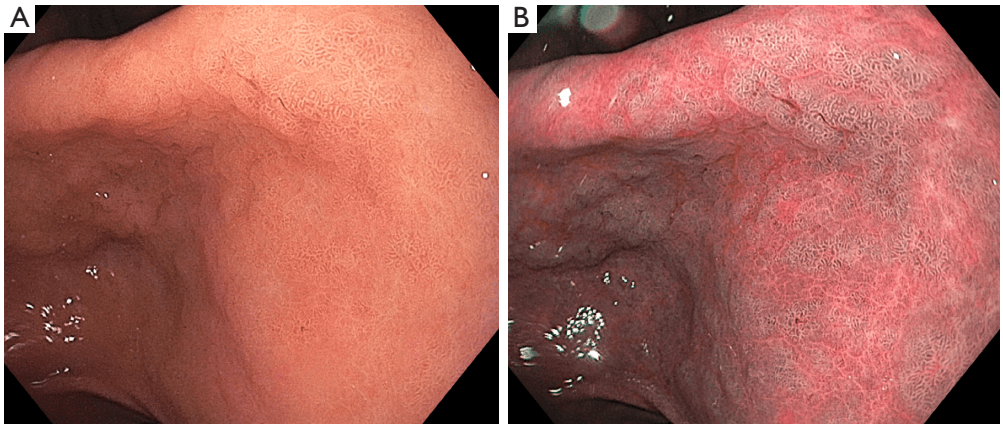

Figure 1 A comparison of white light (A) and narrow band imaging (B) taken from the antrum of a patient with moderate-to-severe gastric intestinal metaplasia. Narrow-band imaging features of metaplasia include the presence of light blue crests (which can be seen throughout the image) as well as the presence of tubulovillous mucosa (which can be seen at the 2 o'clock position).

blue (415 nm) and green (540 nm). Hemoglobin absorbs blue and green light specifically, thus allowing for enhanced visualization of the superficial mucosa, submucosal vessels and capillaries through this technique (20). Pimentel-Nunes *et al.* proposed a simplified classification of gastric lesions with NBI (21,22). In this classification, normal gastric mucosa is identified by a regular circular pattern surrounded by thick and regular vessels, in the antrum and body respectively. GIM is characterized by regular ridge pattern or tubulo-villous mucosa. Light blue crests are slightly raised areas with white-blue coloration that also suggest GIM (*Figure 1*) (23). Dysplasia can be characterized by irregular mucosa and vessels, and a white opaque substance (21,22).

Multiple studies have shown the superiority of NBI over traditional WLE to accurately diagnose precursor lesions. One prospective blinded clinical trial with 112 study participants demonstrated that NBI examination improved diagnostic yield compared to high-definition WLE (65% *vs.* 29%) (24). Even in the setting of autoimmune gastritis (with its corpus-predominant inflammation), NBI examination appears to be highly sensitive for GIM detection (25). Another multicenter prospective study across five countries showed higher sensitivity for diagnosis of dysplasia with NBI compared to WLE (92% *vs.* 74%) (22). In addition to lesion identification, NBI has been shown to be able to predict advanced operative link on GIM (OLGIM) stages with a sensitivity of 89% and specificity of 95% (26). Advanced stages OLGIM are associated with increased risk of the development of gastric neoplasia (27).

Blue-laser imaging (BLI) and linked color imaging (LCI)

Recently, there have been advances in other IEE techniques. One modality is BLI (*Figure 2*). This system features two laser wavelengths in the blue spectrum (450 and 410 nm), producing brighter high-resolution images of the superficial mucosal microvessel structures (28-30). A brighter version of BLI has also been developed, termed BLI-bright (31). A recent randomized control trial showed the superiority in the detection of early cancer of BLI-bright mode compared to WLE (93% *vs.* 50%) (32).

Another IEE modality is LCI. LCI technology utilizes blue, green and red color information and enhances the color contrast after processing (33). A major advantage of LCI is its brightness, which allows for excellent visualization of even distant mucosa—such an attribute is useful in a large lumen organ such as the human stomach (34). The stark color contrast makes early recognition of NCGA precursors easier, with early cancer having an orange-red color, and GIM having a purple color (33,34). One retrospective study comparing indigo carmine chromoendoscopy, BLI, and LCI showed that LCI was significantly better at identifying early differentiated cancers (35). Ono *et al.* demonstrated that the sensitivity of the "lavender color sign" for GIM with LCI was higher than the "whitish flat elevation" seen in WLE (91% *vs.* 19%) (36). Future studies will need to be performed to determine whether BLI and LCI can stratify

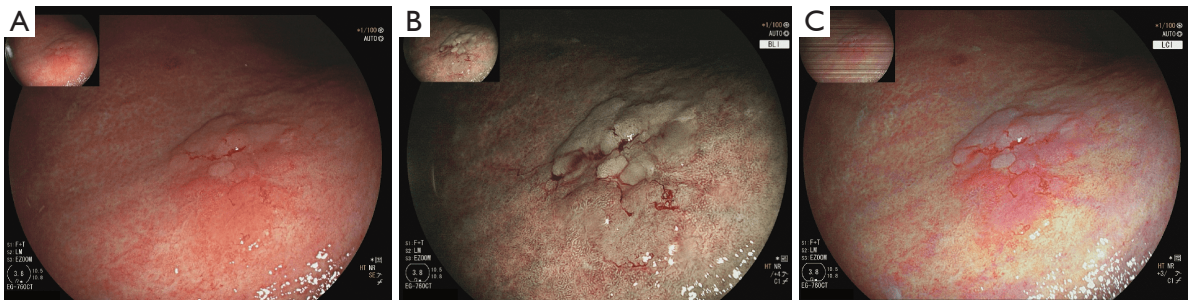

Figure 2 Comparison of white light visualization (A), blue-laser imaging (B), and linked color imaging (C) of an early gastric cancer. Both blue-laser imaging and linked color imaging have demonstrated superior performance characteristics compared to white light endoscopy for the detection of early gastric cancer.

the severity of precursor lesions.

Chromoendoscopy

Chromoendoscopy is a technique that applies topical chemical stains or pigments onto the gastrointestinal tissue. By adding the stain, there is enhanced visualization and localization of the mucosa (37). Chromoendoscopy has long been utilized by gastroenterologists to improve the visualization of the gastric mucosal surface. As early as 1969, Kimura and Takemoto used Congo red staining to define the atrophic border (separating AG from normal mucosa), and used the extent of this line (named the Kimura-Takemoto line) to define a scoring system for AG (38). In modern practice, spray catheters are utilized to deliver the pigment with an even distribution to the entire mucosal surface or a targeted region during endoscopy (39). A variety of staining agents can be utilized with chromoendoscopy and are classified based on their mechanism of action. The three categories are absorptive, contrast, and reactive stains (40).

The absorptive agents, such as methylene blue, are only actively absorbed across the cell membrane for specific cell types (40,41). For example, methylene blue selectively stains the epithelium in the small intestine and colon, as well as intestinal-type metaplasia located in esophageal and gastric mucosa (40-42). This allows for increased detection and evaluation of the anatomical extent of precursor lesions (41,43).

Contrast stains enhance the surface irregularities as the dye collects into the mucosal crevices. Indigo carmine is a commonly-used contrast stain that has a deep blue color (39,40). Studies have shown that indigo carmine combined with acetic acid had better diagnostic outcomes and identification of tumor borders compared to traditional endoscopy or chromoendoscopy with only acetic acid or indigo carmine (44,45). Acetic acid is a weak acid that splits disulfide bonds, thereby disrupting the mucous layer and causing a reversible intracellular protein denaturation. A white discoloration, known as the "acetowhite reaction", occurs due to increased opacity of the surface and allows for improved visualization. This reaction is more prominent in the columnar epithelium, and dysplastic tissue reverses back to the red coloration more quickly than normal epithelium. Acetic acid chromoendoscopy has been shown to delineate the extent of GIM and dysplasia in the esophagus and cervix (46-48).

Reactive stains act by changing color after undergoing a chemical reaction with specific cellular components. Specifically, when Congo red dye is administered to the acidic gastric cells, it transforms from red to a dark blue or black color (39,40). Congo red can be used to detect achlorhydria, and it can also be utilized in conjunction with methylene blue to increase the rates of detection for early cancers (49-51). Dinis-Ribeiro *et al.* noted that magnifying chromoendoscopy with methylene blue had a sensitivity of 76% and 97% for diagnosis of GIM and dysplasia, respectively (43). A comparison study of 33 GIM patients showed a sensitivity of 64% for chromoendoscopy and 42% for standard endoscopy (41). In addition to screening for GIM, methylene blue can also be useful in predicting advanced OLGIM stages, with a sensitivity of 89% and specificity of 92% (52). Despite studies on the efficacy of chromoendoscopy showing promising results in terms of early detection and sensitivity, there have been practical limitations of its

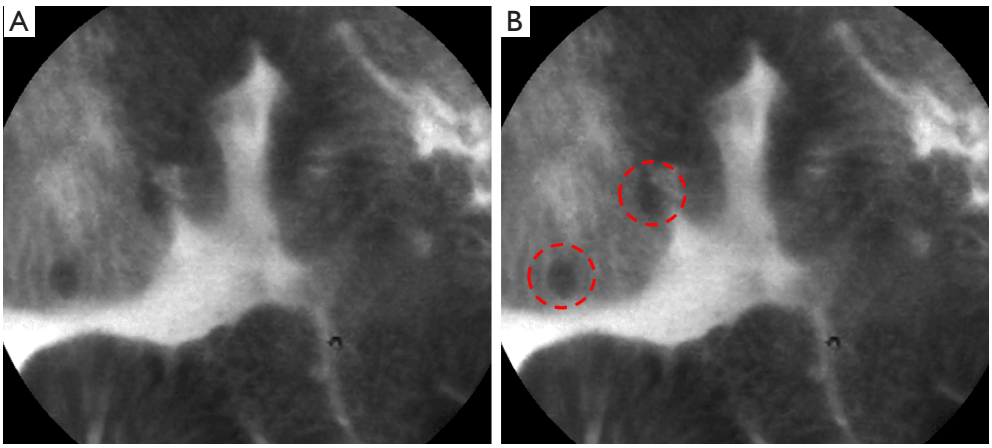

Figure 3 Visualization of gastrointestinal mucosa with confocal endomicroscopy. (A) An image of gastric intestinal metaplasia visualized using confocal endomicroscopy. (B) Gastric intestinal metaplasia can be identified by the appearance of dark-appearing goblet cells (red circles), villous-like foveolar epithelium, and columnar absorptive cells.

implementation, including the time-intensive nature of stain application during procedures (43-45,53).

Confocal laser endomicroscopy

Probe-based confocal laser endomicroscopy (pCLE) provides very high-resolution magnification of the gastrointestinal mucosa and tissue architecture at a cellular and subcellular level. A low power laser shines on the tissue at a specific depth and the reflection of fluorescent light passes through a pinhole to the detector. The pinhole allows the light from only one focal plane to be detected (54,55). Fluorescein dye is added either topically or intravenously. Topical fluorescein, such as acriflavine, stains the cell nuclei of the superficial epithelial layer. However, concerns of possible mutagenic effects have limited its use in clinical practice. Currently, intravenous fluorescein is most commonly used, due to its safety profile and ability to stain both the surface epithelium and the subepithelial layers (54-58). GIM can be identified with dark appearing goblet cells, villous-like foveolar epithelium, and columnar absorptive cells (*Figure 3*) (59).

During an endoscopic procedure, a pCLE miniprobe is introduced through the accessory channel of a standard endoscope. This allows for increased flexibility, and simultaneous utilization of IEE techniques other than WLE (55,60,61). Thus, pCLE is advantageous as an "optical biopsy" that precludes the need for tissue excision. However, some limitations include the need for fluorescein administration, interobserver variability, and the initial learning curve for identifying mucosal features (62). Pittayanon *et al.* reported 80% accuracy after two teaching sessions for beginner learners. The beginner endoscopists underwent four different teaching sessions each 2-week apart, and accuracy was based on the number of correct answers from 20 different pre-selected pCLE images (63). When compared against other imaging modalities, one prospective comparison showed pCLE to be more sensitive (91%) in diagnosing GIM compared to conventional WLE (37%) and NBI (68%) (64). One meta-analysis of 23 Asian studies reported pCLE to demonstrate a pooled sensitivity of 91% for cancer, 92% for GIM, and 81% for dysplasia (65). In addition, pCLE is more precise in detecting the margins of early cancer during endoscopic submucosal dissection (ESD) compared to WLE with chromoendoscopy. Thus, pCLE is a good tool for screening gastric precursors and determining the extent of disease.

Auto-fluorescence imaging (AFI)

AFI detects the natural fluorescence from tissue. After exposure to different wavelengths of light, the endogenous fluorophores from the tissue (such as collagen, elastin, and porphyrin) emit longer wavelengths that can be detected. Each fluorophore has a distinct excitation and emission spectrum. In AFI, the tissue is exposed to excitation blue light and green light. The images from AFI are integrated and processed, such that the normal mucosa is seen as green and dysplastic mucosa as purple (66,67). The dysplastic tissue has reduction in auto-fluorescence due to the loss

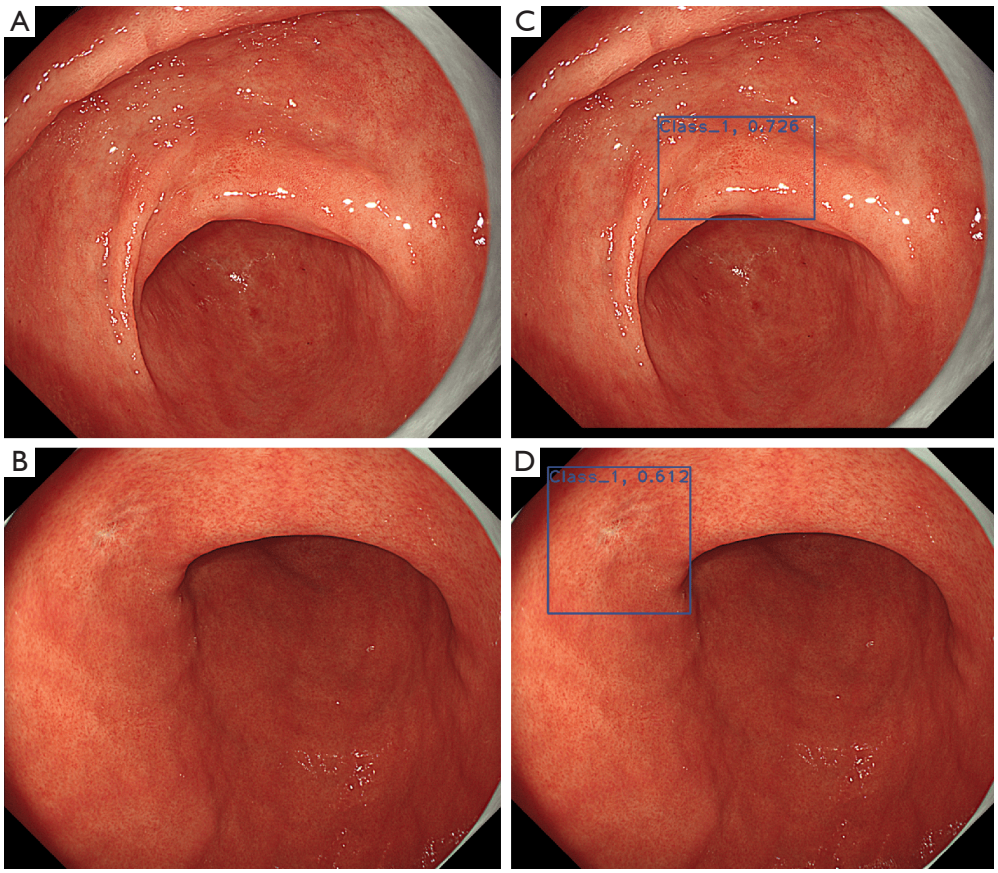

Figure 4 AI utilizes computer algorithms with the ability to perceive, synthesize, and infer information to aid real-time endoscopic visualization. Figures from the top left (A) and bottom left (B) depict antral lesions from two individuals. The AI algorithm outputs a confidence score related to the visual similarity of the lesion in the image compared to the many annotated lesions on which the AI has been trained [top right (C) and bottom right (D), respectively]. In this case, both lesions were found to be cancerous on histology. Images were obtained from the Cancer Institute Hospital of the Japanese Foundation for Cancer Research, and provided courtesy of AI Medical Service Inc., Tokyo, Japan. AI, artificial intelligence.

of collagen, increase in nucleus to cytoplasm ratio, and neovascularization (67,68). Some disadvantages of AFI include the large number of false positive results, and inability to visualize deeper levels of the tissue (69). Some experts suggest that AFI can be used to initially screen suspicious lesions and be used in combination with other imaging modalities.

Artificial intelligence (AI)

There has been much recent interest in the application of AI to improve both the diagnosis of precursor lesions and NCGA. AI utilizes computer algorithms with the ability to perceive, synthesize, and infer information to aid real-time endoscopic visualization after being trained on large annotated data sets (*Figure 4*). Recent trends and development show potential for high rates of image recognition accuracy in the field of gastrointestinal endoscopy. Integrating AI for image recognition could potentially mitigate the interobserver variability and learning curves of different endoscopic imaging modalities. For precursor lesions, one study demonstrated AI to have 92% sensitivity and 86% specificity for detecting GIM after being exposed to a training set of 1,880 NBI and magnified NBI images (70). Zhang *et al.* designed a neural network-based model trained on 3,042 AG images and 2,428 non-AG images, with an observed sensitivity of 95% and specificity of 94% for diagnosing AG (71). With regards to diagnosing cancers, Hirasawa *et al.* trained a convolutional neural network based on 13,584 images of cancer and evaluated

the algorithm on 2,296 stomach images collected from 69 consecutive patients with 77 cancers (some individuals had synchronous tumors). In the validation set, the algorithm demonstrated 92% sensitivity (detecting 71 of 77 cancers), while also identifying 161 non-cancerous lesions as cancer (for a positive predictive value of 31%) (72). In addition, AI has been used to predict tumor invasion depth with great accuracy (above 90%) for multiple imaging modalities (73).

Surveillance

Until relatively recently, there were few guidelines to direct clinicians in the surveillance of gastric precursors. As a result, the decision to survey, and surveillance intervals, were highly variable across practices. However, over the recent few years a number of important clinical guidelines from both the US and Western Europe have begun to place gastric precursor surveillance within a normative framework. While containing modest differences, these guidelines serve to complement one another. Moreover, these guidelines uniformly recommended a stratified approach to surveillance focused on high-risk individuals, based on individual factors, anatomic extent, or histologic features.

Surveillance guidelines for GIM

In the US, the first guideline dedicated toward GIM management was published by the American Gastroenterology Association (AGA) in 2020 (74). While the guideline recommends against routine GIM surveillance endoscopy, high-risk individuals (specifically patients with incomplete or extensive GIM, family history of NCGA, racial/ethnic minority status, or immigration from high-incidence regions) may reasonably elect for endoscopic surveillance with 3–5 years intervals. It is important to note that the AGA guideline emphasizes the role of shared decision-making between physician and patient, adequate patient counseling on the potential but uncertain benefit of surveillance (cancer mortality reduction), as well as the potential risks of endoscopy.

In Europe, the "Management of epithelial precancerous conditions and lesions in the stomach" (MAPS II) guideline (16) was published in 2019, and represents an update to the original 2012 MAPS (75) statement. Individuals with single-site GIM with high-risk features (family history, incomplete GIM, persistent Hp) or patients with severe AG or GIM of both antrum and body should be offered surveillance endoscopy in 3 years. In addition, the British Society of Gastroenterology (76) and Italian multi-society (77) guidelines, both published in 2019, are concordant with the MAPS II guideline (76,77).

Compared to the AGA guideline which emphasizes shared decision-making, European guidelines offer more defined surveillance intervals based on individual-level risk factors (e.g., family history), disease extent, and histologic severity. By contrast, the US guideline emphasizes the role of race, ethnicity, and immigration history—perhaps reflective of the disease burden within the multi-ethnic US population. In whole, US and European guidelines serve to complement each other, and offer for the first time a normative framework for surveillance of gastric precursors.

Surveillance of dysplasia

A consensus is similarly emerging regarding the management of gastric dysplasia. The 2015 American Society for Gastrointestinal Endoscopy Standards of Practice document recommends close-interval (less than 1 year) surveillance of low-grade dysplasia (LGD) with topographic mapping, though a precise interval was not given (78). For high-grade dysplasia (HGD), prompt endoscopic or surgical resection is recommended (78). The European MAPS II guideline states that individuals with dysplasia in the absence of an endoscopically defined lesion should undergo immediate high-quality endoscopic reassessment by IEE. If a lesion is detected on this enhanced examination, prompt endoscopic resection and staging should be performed, as a significant number of dysplastic lesions may be upstaged to cancer on resection. If a lesion is not detected on second examination, Sydney protocol biopsies should be obtained (for AG/GIM staging), and endoscopic surveillance should be performed in either 6 months (for HGD) or 12 months (for LGD) (16). The British guideline recommends that patients with both non-visible LGD and HGD should undergo a second endoscopy, with IEE technique and extensive biopsy sampling. In cases of LGD, if no visible lesion is seen on this repeat examination, surveillance endoscopy should be performed within 1 year. If there is persistent, non-visible LGD seen, endoscopy should be performed annually thereafter. In cases of HGD, if no visible lesion is seen on this repeat examination and HGD persists, surveillance should be performed at 6-month intervals. Moreover, HGD should be discussed with a multi-disciplinary cancer team and

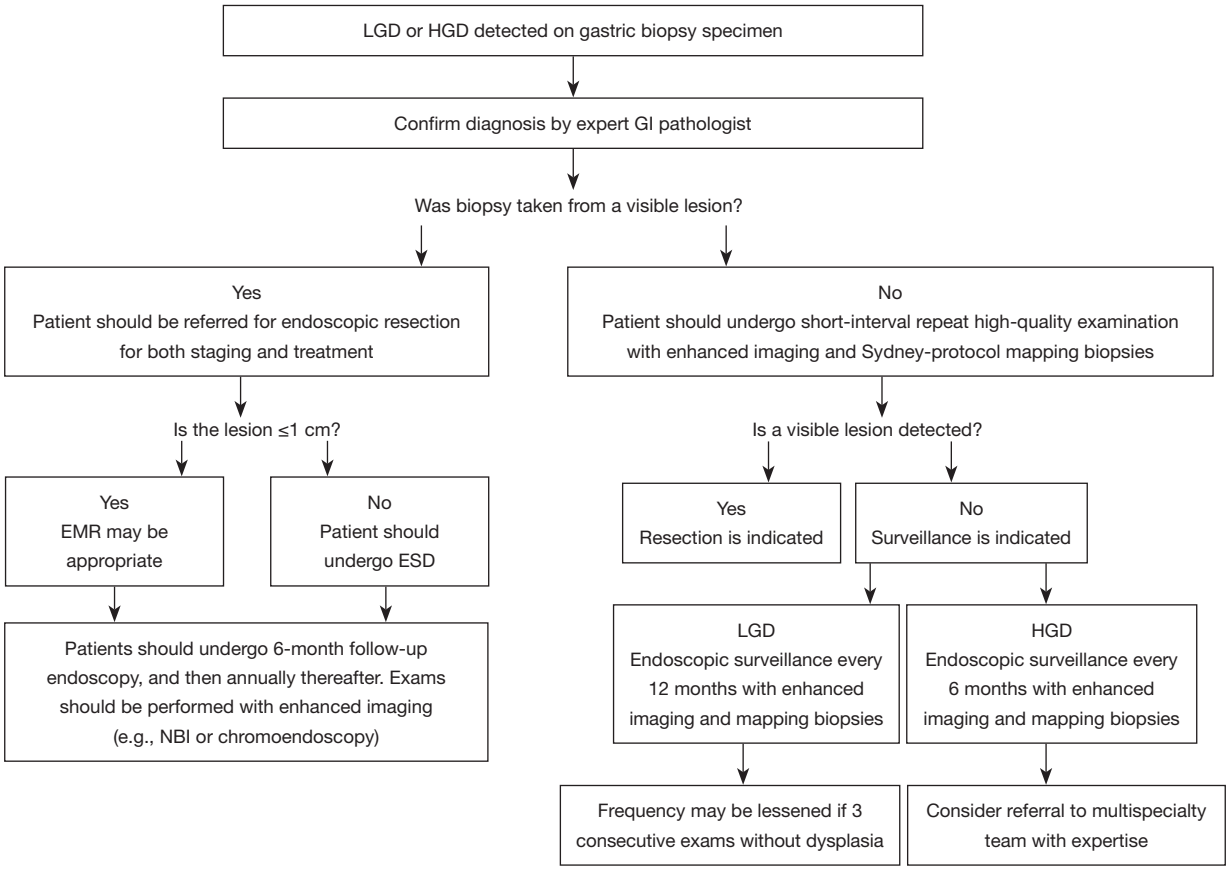

Figure 5 Our suggested management algorithm for gastric dysplasia, based on American Society of Gastrointestinal Endoscopy (78), European MAPS II (75), and British Society (76) guidance. LGD, low-grade dysplasia; HGD, high-grade dysplasia; GI, gastrointestinal; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; NBI, narrow-band imaging; MAPS II, Management of epithelial precancerous conditions and lesions in the stomach.

referred to a clinician with appropriate expertise. Visible dysplasia should undergo *en-bloc* endoscopic resection; an endoscopic mucosal resection (EMR) technique can achieve *en-bloc* excision for lesions ≤10 mm in size, but only an ESD technique can ensure *en-bloc* excision for lesions >10 mm in size. The British guideline also suggests that a follow-up endoscopy 6 months after ESD or EMR of neoplasia, and if no subsequent lesions are identified, annually thereafter (76). Based on a synthesis of these guidelines, we propose a management algorithm for gastric dysplasia in *Figure 5*.

Future risk stratification strategies

Future molecular-based methods may revolutionize the practice of endoscopic surveillance of gastric precursors. One study based on a combined Dutch and Norwegian cohort assessed the role of family history, lifestyle factors, and several serologic biomarkers (including Hp antibody, gastrin-17, pepsinogen, and several pre-selected single nucleotide polymorphisms) on risk for progression (defined as upstaging of operative link score) over a median of 48 months of follow-up (79). The minor allele (C) on TLR4 (rs11536889) was inversely associated with progression of GIM. In a large Singaporean cohort study of a high-risk ethnic Chinese population, several gastric tissue genomic features, including shortened telomere length and chromosomal alterations, were associated with increased risk of progression from GIM to subsequent dysplasia or NCGA (80). Both germline and somatic markers may therefore be used in the future as a supplement to clinical information to risk stratify patients with gastric precursors.

Conclusions

NCGA remains a burden to the world, and a leading source of global cancer mortality. Recognizing, detecting, and appropriately surveying precursor lesions (AG, IM, and dysplasia) is an opportunity to intercept NCGA and potentially prevent hundreds of thousands of deaths each year. Tremendous recent advances in endoscopic imaging technology offer the ability for endoscopists to more accurately identify and more precisely classify gastric precursors. Concurrently, publication of several important recent guidelines now places surveillance of gastric precursors within a normative framework for the first time. Integration of emerging technologies such as AI and biomarkers into high-quality clinical practice may further improve our ability to improve early detection of this highly-fatal cancer.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All clinical procedures described in this study were performed in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patients for the publication of this article and accompanying images.

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