

# Strategies to Optimize Early Endoscopic Detection of Gastric Cancer

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## Abstract

The impact of gastric cancer on the Colombian population is alarming. It is essential to promote strategies that enhance early detection by leveraging available diagnostic tools. This approach can significantly improve patient outcomes. This article presents methods aimed at enhancing the quality of endoscopic procedures and providing key insights to facilitate accurate interpretation of endoscopic findings. The goal is to establish a solid foundation for the precise identification of malignant or precancerous lesions, ultimately leading to better clinical outcomes for this patient population.

## Keywords

Stomach Neoplasms, endoscopy.

## INTRODUCTION

Gastric cancer (GC) is currently a global health problem, ranking fifth in incidence and fourth in cancer-related mortality<sup>(1)</sup>. In Colombia, as of 2020, the incidence was 8,214 cases, and it stood out as the leading cause of death from neoplastic diseases, with 6,461 deaths, reaching a national average of 5.26 deaths per 100,000 inhabitants<sup>(1,2)</sup>. Notably high mortality rates were reported in departments such as Boyacá and Nariño, with 13.38 and 15.72 deaths per 100,000 inhabitants, respectively, in 2014<sup>(3,4)</sup>. In addition, the prognosis in Colombia is concerning. Survival rates for the 2010-2014

period ranged from 15.4% to 18.8%<sup>(5)</sup>. In fact, Santander reported a five-year survival rate of only 11%<sup>(6)</sup>. These grim figures stand in stark contrast to the global cancer survival surveillance data (CONCORD-3), where low-incidence countries like the United States have an estimated survival rate of around 30%, and high-incidence countries such as Korea and Japan reach nearly 70%<sup>(7)</sup>.

This raises an urgent question: what are we doing differently? While acknowledging Colombia-specific risk factors, such as the high prevalence of *Helicobacter pylori*<sup>(8)</sup>, a critical component must be considered: the low detection rate of early gastric cancer (EGC).

## IMPORTANCE

The label of early gastric cancer (EGC), defined as an adenocarcinoma limited to mucosa and submucosa regardless of lymph node involvement<sup>(9)</sup>, is perhaps the one with the greatest impact on patient prognosis. The 5-year survival rate for EGC in recent series exceeds 90%<sup>(10)</sup>, whereas for advanced gastric cancer, it can be as low as 11%.

In Western countries, the detection rate is low. In Japan, up to half of all gastric adenocarcinoma resections are performed for EGC, while in South Korea, the rate ranges between 25% and 30%<sup>(11-13)</sup>. In contrast, in North America and Europe, EGC accounts for only 15% to 21% of detected gastric adenocarcinomas<sup>(12-14)</sup>. In Latin American countries such as Peru and Colombia, detection rates are 15.6% and 21.5%, respectively<sup>(15,16)</sup>.

This significant gap has been attributed to factors such as the higher incidence of EGC in East Asia and differences in the interpretation of gastric histology in Asian centers<sup>(17)</sup>, factors that are difficult to modify. However, other important variables can be addressed, such as the implementation of early detection programs. For example, Japan increased EGC detection from 15% to 57% following the introduction of screening programs<sup>(11,12)</sup>. Another actionable factor is the improvement of the quality and interpretation of upper gastrointestinal endoscopy (UGE) to enhance the detection of EGC and precursor lesions. The miss rate for EGC during UGE can be as high as 25% in Western studies, and among endoscopists with less than 10 years of experience, this rate may reach up to 32.4%<sup>(18)</sup>.

Innovative methods are currently being developed to further improve detection. Among them, gastric endoscopy stands out as one of the new endoscopic techniques. It offers ultra-high magnification, allowing cellular-level visualization of the gastrointestinal mucosa and enabling a more detailed prediction of malignancy risk<sup>(19)</sup>. Additionally, the development of artificial intelligence programs has surpassed the EGC detection rate of expert endoscopists<sup>(19)</sup>. Non-invasive methods are also emerging as promising tools for early EGC detection, including circulating tumor DNA (ctDNA) biomarkers, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs)<sup>(20)</sup>.

In contrast, in Colombia, despite alarmingly high mortality rates, strategies already described in the literature to increase EGC detection have not been consciously and systematically adopted. Therefore, the objectives of this article are to raise awareness among Colombian physicians and to present, in a concise and straightforward manner, useful strategies for increasing EGC detection in the country.

## GASTRIC CANCER SCREENING

Regarding screening, countries with a high incidence of gastric cancer (>20 per 100,000 inhabitants), such as South Korea and Japan, perform UGE every two years starting at the ages of 40 and 50, respectively<sup>(21-23)</sup>. Some Colombian authors have proposed adopting these strategies at a national level<sup>(24)</sup>; however, the clinical practice guidelines of the Colombian Association of Gastroenterology and the National Cancer Institute of Colombia conclude that there is insufficient evidence to make a recommendation on this matter<sup>(25,26)</sup>. As a result, they maintain only the same recommendations for primary prevention, monitoring precursor lesions, and performing UGE in patients with uninvestigated dyspepsia over the age of 35<sup>(25,26)</sup>. These sole recommendations are established because screening programs are not sustainable in countries with developing economies<sup>(27)</sup>.

Additionally, as proposed by Januszewicz et al., early detection strategies should be adapted based on the incidence in a given region. In Colombia, a country with an intermediate incidence (10-20 per 100,000 inhabitants), nationwide screening programs are not supported in terms of cost-effectiveness<sup>(27)</sup>. However, the identification of high-risk subpopulation should be considered, so they can be included in early detection programs. These programs should include active screening and eradication of *H. pylori*, and, as suggested by Januszewicz et al., existing screening programs, such as Colombia's colorectal cancer screening program, in which all individuals over the age of 50 undergo colonoscopy, should be leveraged. This represents an opportunity to perform UGE simultaneously<sup>(27)</sup>. In this way, early evaluation can be achieved, leading to the detection of either EGC or precursor lesions, allowing for resection of the former or close follow-up of the lesions.

## STRATEGIES TO IMPROVE THE QUALITY AND INTERPRETATION OF UPPER GASTROINTESTINAL ENDOSCOPY FOR THE DETECTION OF EARLY GASTRIC CANCER

As the American Robert Schuller once said, "Spectacular achievement is always preceded by unspectacular preparation." Seemingly minor details, such as proper preparation, should not be underestimated, as they are essential to achieving optimal visualization of the gastric mucosa. The following key points have been proposed to support this goal.

### Use of mucolytics and defoaming agents

Foam and adherent mucous content hinder proper visualization of the gastric mucosa. Therefore, in Japan, pronase is

systematically used as a mucolytic, in combination with the defoaming agent dimethylpolysiloxane<sup>(26)</sup>. In Colombia, due to the unavailability of these drugs, an alternative mixture has been recommended. It consists of 100 mL of water mixed with 2 mL of acetylcysteine (200 mg/mL) and 0.5 mL (40 mg/mL) of dimethicone, administered 30 minutes before the procedure<sup>(28)</sup>. This has been shown to improve visualization of the gastric mucosa, optimize procedure time, and enhance endoscopist satisfaction<sup>(29)</sup>.

### Use of antiperistaltic agents

Constant peristaltic movement within a cavity characterized by multiple folds, curvatures, and variable distensibility can hinder the visualization of small lesions. Therefore, although there is no current evidence showing that this measure increases the detection of EGC, its use is recommended in cases of intense peristaltic activity<sup>(28)</sup>.

The options include:

- Hyoscine butylbromide (10-20 mg intramuscular [IM] or intravenous [IV], single dose).
- Glucagon (1 mg IV, single dose).
- Peppermint oil (20 mL of 0.8% sprayed directly as an aerosol).

Hyoscine, which is readily available and low-cost, should be avoided in patients with glaucoma, prostatic hyperplasia, severe heart disease, or paralytic ileus<sup>(28)</sup>. Glucagon, in contrast, has a safe cardiovascular profile but is more expensive, less available, and contraindicated in diabetic patients or those with a history of pheochromocytoma. Peppermint oil is the safest option but is expensive and not widely available<sup>(28)</sup>.

### Adequate insufflation

Proper insufflation of the gastric chamber is essential to fully expose the mucosa and to avoid missing lesions hidden among the gastric folds. But what exactly constitutes adequate insufflation during UGE? In laparoscopic surgery, insufflation is pressure-controlled, which optimizes visualization and helps prevent adverse effects. In contrast, gastroenterologists rely on subjective assessments. Inadequate insufflation may result in missed lesions, whereas over-insufflation may lead to secondary complications, ranging from mild issues, such as post-procedural distension or pain, to more severe outcomes, including Mallory-Weiss or Boerhaave syndrome due to barotrauma. There is a lack of literature and evidence to determine the optimal pressure. However, preliminary findings showed that an average pressure of 10 mm Hg in the gastric cavity was well tolerated by endoscopists, allowing lesion detection without adverse effects<sup>(30)</sup>.

### Visualization time

Inevitably, the more time spent observing a given area, the more precisely it will be examined, thus increasing the likelihood of detecting a lesion, including EGC. This hypothesis, tested by Teh et al., demonstrated that the “slow endoscopist” (with an average UGE duration of 8.6 minutes) is three times more likely to detect a neoplastic lesion (cancer and dysplasia only) in the stomach compared to a “fast endoscopist” (with an average UGE duration of 5.5 minutes; odds ratio [OR]: 3.42; 95% confidence interval [CI]: 1.25-10.38)<sup>(31)</sup>. Notably, the European Society of Gastrointestinal Endoscopy (ESGE) includes a minimum duration of 7 minutes from endoscope insertion to removal as a quality indicator<sup>(32)</sup>.

### Remembering blind spots

A number of areas are commonly overlooked during the evaluation of the gastric mucosa. Therefore, it is essential to consciously assess these points<sup>(33)</sup>:

- Cardia (angle of His).
- Greater curvature of the proximal gastric body.
- Posterior wall of the gastric body.
- Lesser curvature of the antrum.
- Pylorus.

### Photodocumentation

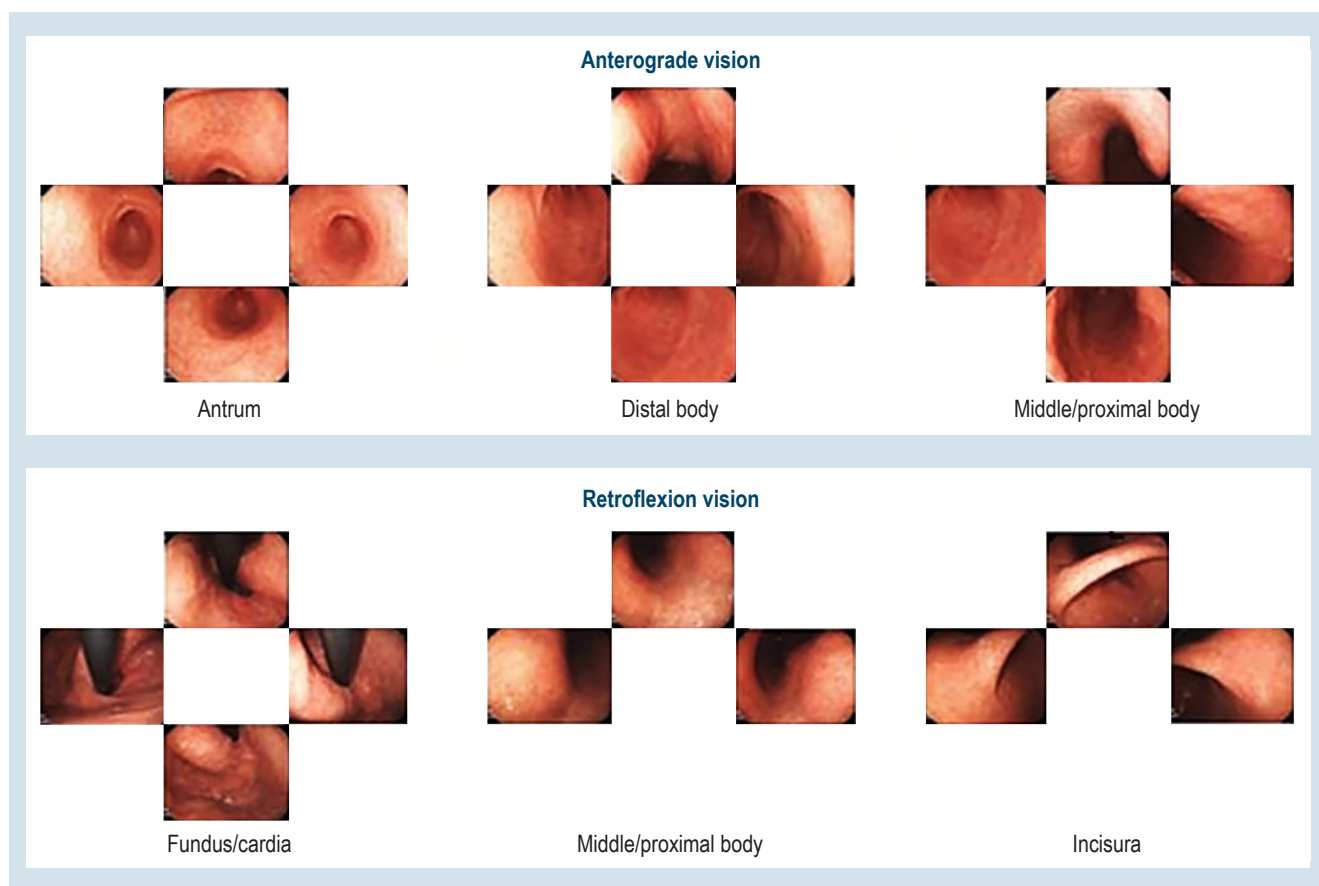
To avoid blind spots during the evaluation of the gastric mucosa, K. Yao, MD, proposed a systematic screening protocol for the stomach (SSS)<sup>(34)</sup>. The SSS begins in the gastric antrum. Using anterograde vision, photos are taken of the four quadrants of the antrum, the distal body, and the middle-proximal body. Then, in retroflexion, photos are taken of the four quadrants of the gastric fundus and the cardia, as well as three photos of the middle/proximal body and the incisura, for a total of 22 endoscopic photos (**Figure 1**).

In this regard, in Colombia, F. Emura, MD, described the systematic alphanumeric-coded endoscopy (SACE), which includes the entire upper digestive tract, evaluating 8 regions and 28 areas (**Figure 2**)<sup>(35)</sup>.

## INTERPRETATION OF ENDOSCOPIC FINDINGS

### Determination of the risk of early gastric cancer development

Chronic gastritis associated with *H. pylori*, gastric atrophy, and intestinal metaplasia are the main risk factors linked to



**Figure 1.** Systematic Screening Protocol for the Stomach (SSS). Adapted from: Toyoshima O, et al. *World J Gastroenterol.* 2020;26(5):466-77<sup>(38)</sup>.

the development of EGC<sup>(36)</sup>. Although these conditions are defined histologically, endoscopic findings that predict such pathologies can be identified during the procedure.

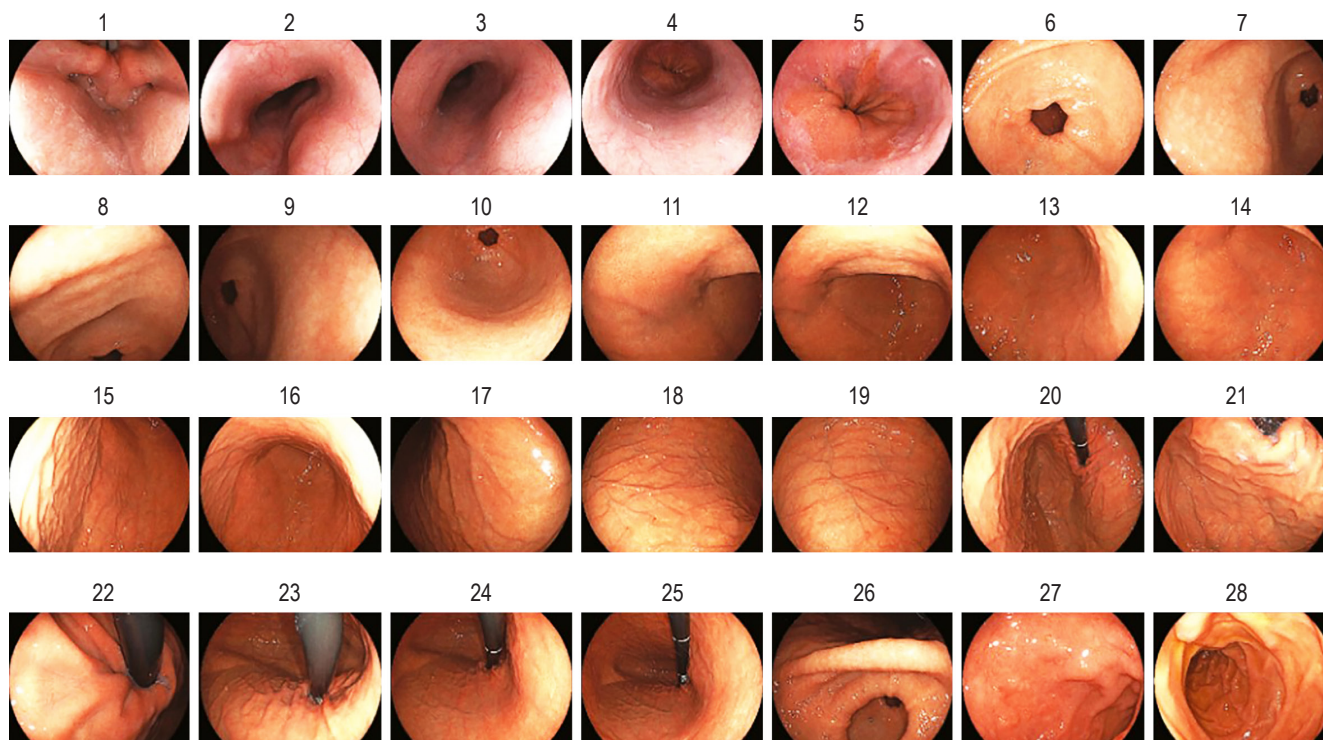
### Gastric atrophy

Atrophy, defined as the loss of glandular tissue, is endoscopically identified by a pale mucosa, visible submucosal vessels, and flattening of the gastric folds<sup>(36)</sup>. The Kimura-Takemoto classification (**Figure 3**), which shows a 69.8% concordance between endoscopic and histological assessment and good reproducibility (weighted kappa of 0.76; 95% CI: 0.71–0.80)<sup>(41)</sup>, allows for grading the severity of atrophy. Severity is based on its extent: mild (C1-C2), moderate (C3-O1), or severe (O2-O3) atrophy predicts the 5-year risk of EGC at 0.7%, 1.9%, and 10%, respectively. Severe atrophy reflects a hazard ratio of 9.3 (95% CI: 1.7–17.4) when compared with no atrophy or mild atrophy<sup>(37)</sup>.

### Gastric intestinal metaplasia

With standard white light endoscopy (WLE), this condition can be identified by the presence of whitish plaques surrounded by mixed areas of pink and pale mucosa, creating an irregular surface appearance<sup>(39)</sup>. However, the diagnostic accuracy of WLE is limited when compared to image-enhanced techniques such as narrow-band imaging (NBI), which detects gastric intestinal metaplasia (GIM) with a sensitivity of 87% versus 53% for WLE ( $p < 0.001$ )<sup>(39)</sup>. The use of NBI is recommended to identify suggestive features such as the “light blue crest” sign, “irregular marginal zone,” and “white opaque substance” (WOS) (**Figure 4**)<sup>(39)</sup>.

It is recommended to classify these findings using the EGGIM score (**Table 1**), based on the percentage of metaplasia (greater or less than 30%) in the antrum, incisura, and body. Each region is scored accordingly, and if the total score exceeds 4, there is a strong correlation with histological severity (OLGIM stage III/IV), with an area under



**Figure 2.** Reconstructed illustration of a Complete Photodocumentation of the Upper Gastrointestinal Tract. **1.** Hypopharynx. **2.** Esophagus, upper third. **3.** Esophagus, middle third. **4.** Esophagus, lower third. **5.** Esophagogastric junction. **6.** Pyloric canal. **7.** Antrum, anterior wall. **8.** Antrum, lesser curvature. **9.** Antrum, posterior wall. **10.** Antrum, greater curvature. **11.** Lower third, anterior wall. **12.** Lower third, lesser curvature. **13.** Lower third, posterior wall. **14.** Lower third, greater curvature. **15.** Middle third, anterior wall. **16.** Middle third, lesser curvature. **17.** Middle third, posterior wall. **18.** Middle third, greater curvature. **19.** Upper third, greater curvature. **20.** Upper third, anteroposterior wall. **21.** Fornix. **22.** Cardia. **23.** Lesser curvature, upper third. **24.** Lesser curvature, middle third. **25.** Lesser curvature, lower third. **26.** Angular incisure. **27.** Duodenal bulb. **28.** Duodenum, second portion. Adapted from: Waddingham W, et al. F1000Res. 2018;7:F1000 Faculty Rev-715<sup>(40)</sup>.

the curve of 0.96 (95% CI: 0.93-0.98) and a sensitivity and specificity of 89% and 95%, respectively<sup>(41)</sup>.

### Chronic *Helicobacter pylori* Gastritis

Multiple endoscopic findings have been described in association with *H. pylori* infection. O. Toyoshima, MD, identified those findings with true statistical significance and proposed the Kyoto classification score<sup>(38)</sup>, which is based on the sum of five endoscopic findings: atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness (**Table 2**). A score  $\geq 2$  indicates active *H. pylori* infection with an accuracy of 82%, and a score  $\geq 4$  suggests an increased risk of gastric cancer<sup>(38)</sup>.

As a protective factor, the presence of a regular arrangement of collecting venules (RAC) in the gastric body has a high negative predictive value and is a reliable endoscopic marker for ruling out *H. pylori* infection<sup>(42)</sup>.

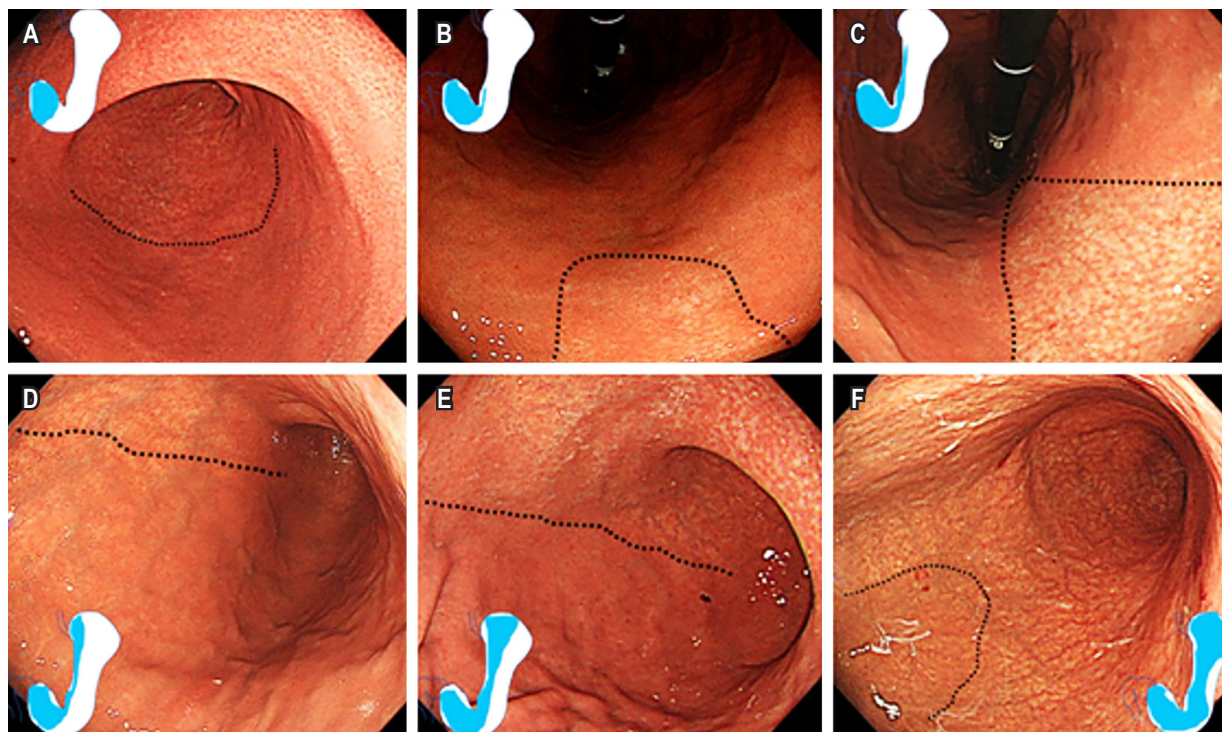
### KEY FINDINGS FOR IDENTIFYING EARLY GASTRIC CANCER

After proper preparation and the identification of risk findings, the next step is to recognize lesions suspicious for malignancy. Polypoid or ulcerated lesions are easily noticeable and generally do not pose a diagnostic challenge for the endoscopist. Here, we focus on outlining guidelines to help detect suspicious neoplastic changes in superficial lesions, which can easily go unnoticed or be mistaken for changes similar to focal gastritis<sup>(34)</sup>.

### Findings with Standard White-Light Endoscopy

If WLE is the initial approach, it is important to be aware of signs suggestive of neoplasia. These include<sup>(43)</sup>:

- Mucosal discoloration (erythema or pallor) or asymmetric color distribution.



**Figure 3.** Kimura-Takemoto classification. **A.** C1 (atrophy is limited to the antrum). **B.** C2 (atrophy is limited to the minor area of the lesser curvature of the body). **C.** C3 (atrophy involves the main area of the lesser curvature of the body but does not extend beyond the cardia). **D.** O1 (atrophy extends to the gastric fundus passing over the cardia between the lesser curvature and the anterior wall). **E.** O2 (the atrophic border of the body compromises the anterior wall). **F.** O3 (atrophy is generalized involving the anterior wall and greater curvature). Adapted from: Toyoshima O, et al. *World J Gastroenterol.* 2020;26(5):466-77<sup>(38)</sup>.

**Table 1.** Endoscopic Grading of Gastric Intestinal Metaplasia

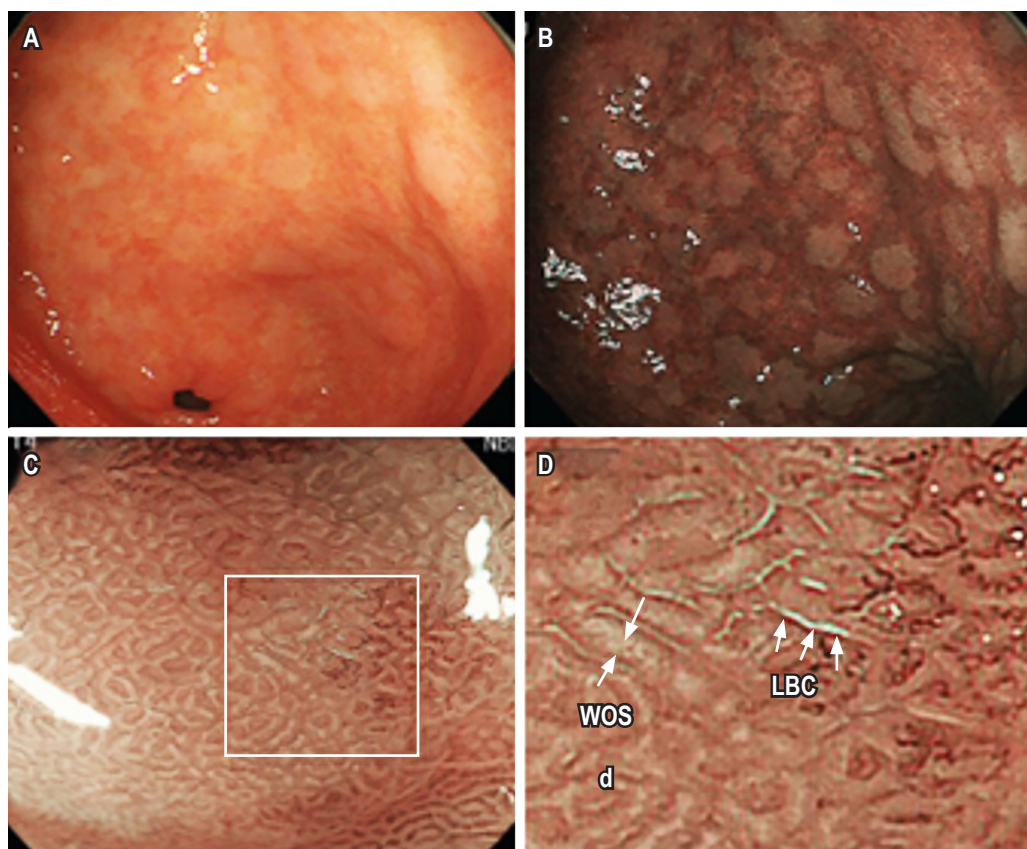
	Lesser curvature of the antrum	Greater curvature of the antrum	Incisura	Lesser body curvature	Greater body curvature
Without GIM	0	0	0	0	0
≤30% GIM*	1	1	1	1	1
>30% GIM*	2	2	2	2	2
GIM Score					

\*Percentage of affected surface area. GIM: gastric intestinal metaplasia. Modified from: Esposito G, et al. *Endoscopy.* 2019;51(6):515-21<sup>(41)</sup>.

- Macroscopically irregular mucosa.
- Confluence of gastric folds.
- Narrow folds or abrupt interruption of folds.
- Localized mucosal opacity.
- Loss of mucosal gloss or changes in light reflection.
- Spontaneous bleeding.

This evaluation alone is insufficient to diagnose small EGC, measuring less than 1 cm. When comparing the diagnostic

accuracy, sensitivity, and specificity of WLE versus magnifying narrow-band imaging (M-NBI), the diagnostic values were as follows: diagnostic accuracy of 90.4% for M-NBI vs. 64.8% for WLE, sensitivity of 60.0% vs. 40.0%, and specificity of 94.3% vs. 67.9%, respectively. The accuracy and specificity of M-NBI were significantly higher than those of WLE ( $p < 0.001$ )<sup>(34)</sup>. The combination of both modalities is superior to the exclusive use of either one<sup>(34)</sup>. Therefore, concomitant use is recommended.



**Figure 4.** Endoscopic Findings of Gastric Intestinal Metaplasia. **A.** White-light endoscopy image with gastric intestinal metaplasia clearly visible as whitish plaques. **B.** Narrow-band imaging enhances mucosal contrast and highlights patches of gastric intestinal metaplasia. **C.** Magnifying endoscopy reveals light blue crests (LBC) on the epithelial surface; in some cases, white opaque substance (WOS) can be seen in the intermediate part of the crypt openings. **D.** Corresponds to the white square in image **C**. Adapted from: Waddingham W, et al. F1000Res. 2018;7:F1000 Faculty Rev-715<sup>(40)</sup>.

**Table 2.** Kyoto Score

Endoscopic findings		Score
Atrophy (Kimura-Takemoto)	C0-C1	0
	C2-C3	1
	01-03	2
Metaplasia	Antrum	1
	Antrum and body	2
Diffuse erythema	Mild with RAC	1
	Severe	2
Thickening of gastric folds (>5 mm)	Absence	0
	Presence	1
Nodular surface	Absence	0
	Presence	1

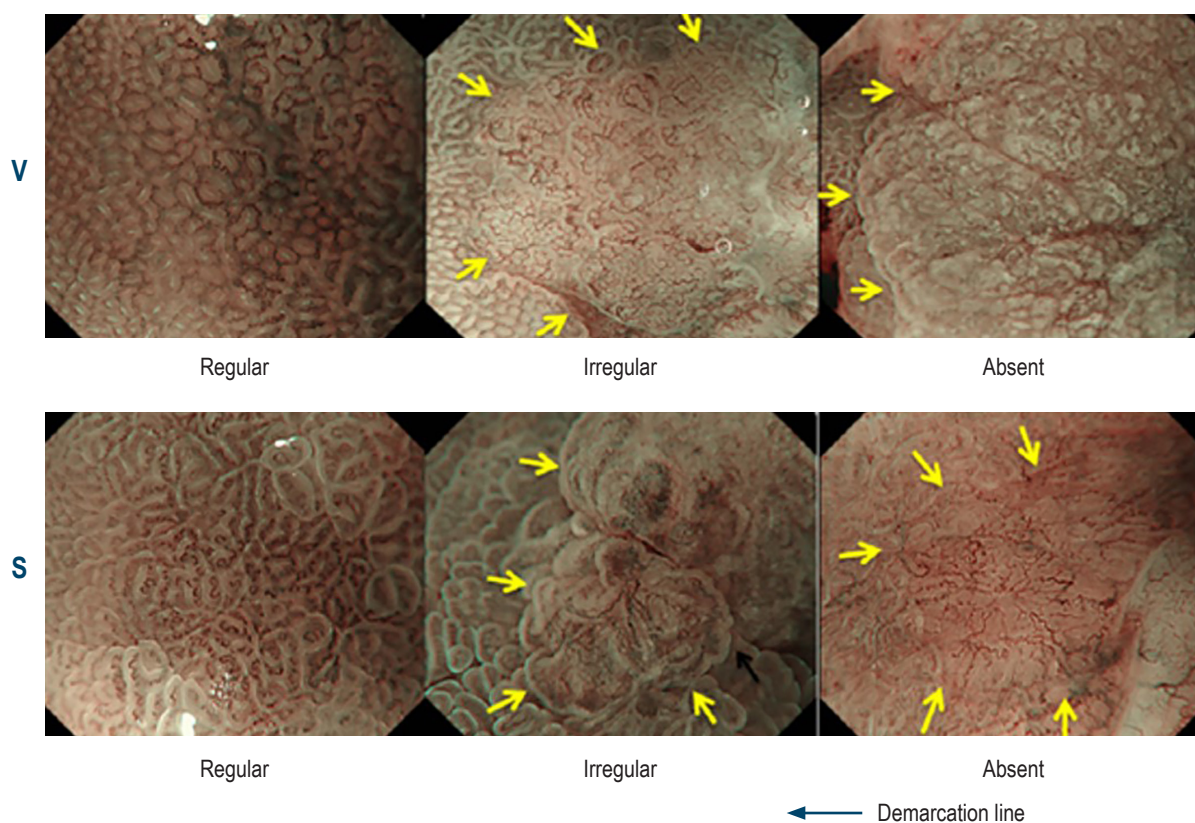
RAC: regular arrangement of collecting venules. Modified from: Toyoshima O, et al. World J Gastroenterol. 2020;26(5):466-77<sup>(38)</sup>.

## Findings with Magnifying Narrow-Band Imaging

M-NBI enables the assessment of the microanatomy of the glandular epithelium. This allows for the identification of a clear demarcation line (DL) between the lesion and the normal mucosa, as well as the evaluation of microvascular (MV) and microsurface (MS) patterns in potentially suspicious lesions. Based on these observations, Yao et al.<sup>(34)</sup> developed the VS (vessel and surface) classification system, which categorizes microvascular and microsurface patterns as regular, irregular, or absent (**Figure 5**).

### Microvascular Pattern

- Regular: mucosal capillaries exhibit a uniform, homogeneous morphology, with symmetrical distribution and regular arrangement.

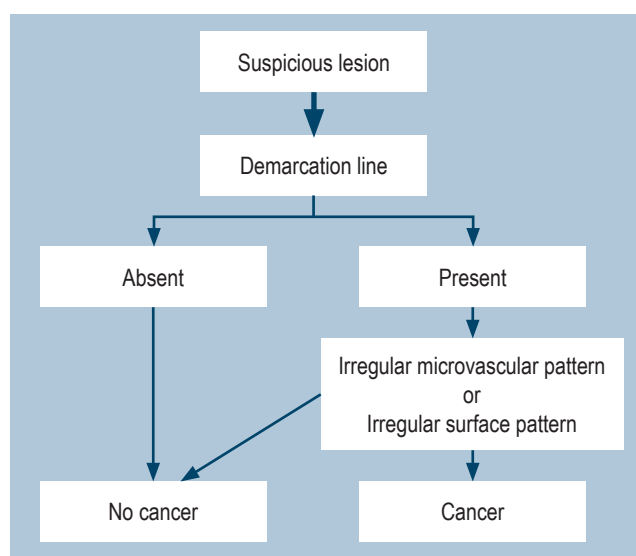


**Figure 5.** VS classification (vessels and surface). Modified from: Yao K. *Ann Gastroenterol.* 2013;26(1):11-22<sup>(34)</sup>.

- Irregular: characterized by heterogeneous morphology, asymmetrical distribution, and irregular arrangement. Tortuous, branched, or aberrant vessels are observed, with or without a network.
- Absent: the subepithelial microvascular pattern is obscured due to the presence of WOS, which prevents proper visualization of the surface.

### Microsurface Pattern

- Regular: the morphology of the marginal crypt epithelium shows a uniform linear/curved/oval/circular structure, with homogeneous and symmetrical distribution, and a regular arrangement.
- Irregular: the marginal crypt epithelium presents a heterogeneous morphology, asymmetrical distribution, and irregular arrangement. When WOS is present in an irregular manner, it may also be interpreted as an irregular microsurface pattern.
- Absent: neither the structure of the marginal crypt epithelium nor the WOS is visible.



**Figure 6.** MESDA-G Diagnostic Algorithm. Modified from: Muto M, et al. *Dig Endosc.* 2016;28(4):379-93<sup>(43)</sup>.

Based on these findings, it was determined that a lesion showing a DL along with either an irregular microsurface or an irregular microvascular pattern can be diagnosed as high-grade dysplasia or EGC, with a diagnostic accuracy of 97%<sup>(43)</sup>. This principle was endorsed by the Japan Gastroenterological Endoscopy Society, the Japanese Society of Gastroenterology, and the Japanese Gastric Cancer Association, and was summarized in the MESDA-G algorithm (Magnifying Endoscopy Simple Diagnostic Algorithm for Early Gastric Cancer) (**Figure 6**)<sup>(43)</sup>. It provides a simple and rapid method for endoscopic identification of EGC.

## CONCLUSION

Colombia is a country with high mortality from gastric cancer, making the implementation of early detection

strategies essential. Achieving high-quality endoscopy that facilitates lesion detection, along with the knowledge required for accurate interpretation of endoscopic findings, will increase the detection of EGC and optimize the follow-up of precursor lesions. This will positively impact the clinical outcomes of the Colombian population affected by this condition.

## Conflicts of interest

The authors declare that they have no conflicts of interest.

## Source of funding

None.

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