



REVIEW

Image-enhanced endoscopy in the diagnosis of gastric premalignant conditions and gastric cancer



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Received 14 June 2022; accepted 20 June 2022

Available online 26 May 2023

KEYWORDS

Gastric premalignant conditions;
Intestinal metaplasia;
Gastric dysplasia;
Early gastric cancer;
Conventional chromoendoscopy;
Magnification endoscopy;
Advanced imaging techniques

Abstract Diagnosis of early gastric cancer and its precancerous lesions remains a challenge for great part of western endoscopists. Changes seen in the mucosal pattern are generally subtle and hence difficult to identify. In this article, we will review the usefulness of conventional and virtual chromoendoscopy and magnification endoscopy in the recognition and classification of these lesions.

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PALABRAS CLAVE

Lesiones precursoras de cáncer gástrico; Metaplasia intestinal; Displasia; Cáncer gástrico precoz; Cromoendoscopia convencional; Endoscopia de magnificación; Técnicas de imagen avanzada

Técnicas de imagen avanzada en la detección y caracterización de las lesiones precursoras del cáncer gástrico y del cáncer gástrico precoz

Resumen La detección del cáncer gástrico precoz y de sus lesiones precursoras constituye un desafío para gran parte de los endoscopistas occidentales. Los cambios morfológicos que se producen en la mucosa gástrica generalmente son sutiles y, por tanto, difíciles de visualizar. En esta revisión se analiza la utilidad de la cromosendoscopia convencional, así como de sus modalidades digitales, y de la endoscopia con magnificación para reconocer y caracterizar estas lesiones.

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Introduction

Although the incidence of gastric cancer in Spain is low (5.8 cases per 100,000 population), the mortality rate is high, due in part to the fact that it is usually detected late.¹

The lack of sufficient precision with use of white light endoscopy and non-targeted biopsies to diagnose the spectrum of malignant and premalignant gastric lesions prompted the development of new techniques, resulting in significant advances in recent years.

Detecting gastric cancer precursor lesions (GCPL) makes it possible to identify patients who require closer follow-up, given their higher likelihood of developing early gastric cancer (EGC).

Improved detection of EGC during upper gastrointestinal endoscopy enables more conservative endoscopic treatments to be carried out, with cure rates comparable to those obtained with surgery.

This narrative review summarises the available evidence on endoscopic diagnosis and the use of auxiliary techniques which improve its performance, such as conventional and digital chromoendoscopy and magnifying endoscopy.

The benefits of the white light image and high definition

In the following sections on GCPL and EGC detection, we review the diagnostic accuracy of high-definition white light endoscopy (HD-WLE) in identifying these lesions. Other relevant aspects in the diagnosis and management of these lesions have already been dealt with extensively in the recent position paper on the quality of endoscopy in GCPL and are not the subject of this review.²

For detection of EGC, the performance of standard resolution imaging with white light (WLE) is limited. In what is now a classic Japanese study using standard resolution endoscopes, the sensitivity of this diagnostic test was only 81%.³

HD-WLE, however, has shown greater diagnostic accuracy in the detection of EGC. In a prospective study comparing HD-WLE to standard resolution with a transnasal endoscope, with HD-WLE 12.2% of lesions were not detected and the incorrect diagnosis rate was 9.8%. These rates were worse

with the standard image, at 26.8% and 14.6% respectively. Of the 41 histologically confirmed cancers, 11 were not detected with non-high-definition endoscopes and three were misdiagnosed as non-cancerous lesions.⁴

Although the HD-WLE results could be considered acceptable, recent studies⁵ have shown low sensitivity when compared to the use of enhancing technologies. Although for the detection of dysplasia the specificity of HD-WLE reached 99%, the sensitivity was clearly lower than that obtained with high definition and narrow band imaging (HD-NBI) (74% vs 92% respectively). In the specific case of EGC with depressed morphology and a diameter of less than 10 mm, in a randomised, multicentre study,⁶ HD-WLE clearly showed improved sensitivity, specificity and diagnostic accuracy (40%, 67.9%, and 64.8% respectively).

Classic chromoendoscopy techniques

Different chromoendoscopy (CE) techniques have been used to increase diagnostic accuracy. The use of different stains allows the morphology of the mucosal surface to be examined in detail, as it is more difficult to study with white light imaging.

The diagnostic efficacy of the different conventional CE techniques and HD-WLE were compared in a meta-analysis which included 10 studies.⁷ A sub-analysis performed to assess the diagnostic accuracy of CE in detecting EGC resulted in 86.6% for CE and 54.9% for WLE. Overall, the sensitivity and specificity of CE for detecting EGC and pre-cancerous lesions were 90% and 82% respectively, with a diagnostic validity of 0.94 measured with the area under the ROC curve (AUROC) value.

Below we review some of the available data regarding the most common conventional CE techniques.

Methylene blue

Methylene blue selectively stains areas of intestinal metaplasia (IM). When used at 1% and with magnification, the sensitivity and specificity were adequate for the diagnosis of dysplasia (97.4% and 81.1% respectively), with a high negative predictive value (99.7%). It is therefore possible to reasonably rule out the presence of advanced lesions when

this stain is used.⁸ In this study, a classification into three groups was used (I: without uptake; II with regular uptake; and III: with heterogeneous uptake and irregular mucosal pattern), which was subsequently validated⁹ and showed 100% sensitivity for detecting dysplasia and 99% specificity, with high interobserver agreement (0.92). The diagnostic validity measured with the AUROC was 0.99.

Acetic acid

Acetic acid (AA) reversibly modifies the structure of cellular proteins, giving rise to a reaction highlighting the architecture of the mucosa by inducing a whiter colouration of the normal mucosa, while the EGC appears pinker. In fact, the early clearance of AA in the mucosa has been associated with the invasiveness of the lesion.¹⁰

CE with AA was used to assess the topographic extension of IM compared to taking biopsies according to the Sidney protocol.¹¹ The use of AA detected 18% of the cases with extensive IM, while the detection rate was only 1% in the group where the stain was not applied. The sensitivity of AA was 94% and the specificity 77%. In this study, 14% of patients had mild side effects related to the use of the stain (epigastric pain or nausea). In terms of the diagnostic accuracy of AA in detecting IM, when combined with NBI, it has shown a higher sensitivity (AA-NBI: 87.9% vs NBI: 66.7%) and a higher negative predictive value (AA-NBI: 84.9% vs NBI: 67.2%) than the use of NBI alone.¹² In this same study, the sensitivity and specificity of HD-WLE were only 33.3% and 28.8% respectively.

Bichromoendoscopy

Bichromoendoscopy (biCE) with AA and indigo carmine (IC) has also been used in the diagnosis of gastric cancer. The addition of IC to the AA accentuates the changes by making the normal mucosa bluish, and the lesion a paler pink.

In a prospective study by Yep-Gamarra et al.,¹³ in which they assessed 50 patients diagnosed with GCPL, routine endoscopy with biCE identified more patients with dysplasia (9 versus 3, $p < 0.05$) and obtained more biopsies with a diagnosis of dysplasia, both in visible lesions (6 vs 0, $p < 0.05$) and invisible lesions (6 vs 3, $p = \text{NS}$).

For the demarcation of EGC margins, in a prospective study carried out by Sakai et al.¹⁴ comparing four types of endoscopic images (HD-WLE, CE with IC, staining with AA and biCE), the diagnostic yield was very poor for the WLE (17%), increased with AA (41.5%) and IC (52.8%), both used alone, and was clearly higher using biCE (94.3%).

In a similar trial, the utility of this mixed stain was more decisive in defining the margins when the lesions had more diffuse borders compared to the use of IC alone (86% had better demarcation of the borders with biCE vs 56% with IC). However, when the lesion already appeared to have well-defined borders with HD-WLE, the use of biCE did not significantly help to obtain a more precise view (100% with IC vs 95% with AA + IC). In fact, combined staining is not useful in all cases. In 3/55 EGC with sharp margins on HD-WLE, the use of biCE was thought to worsen the original image. This is because, in some cases, AA increases the secretion of mucus in the mucosa, thus reducing the contrast between the lesion

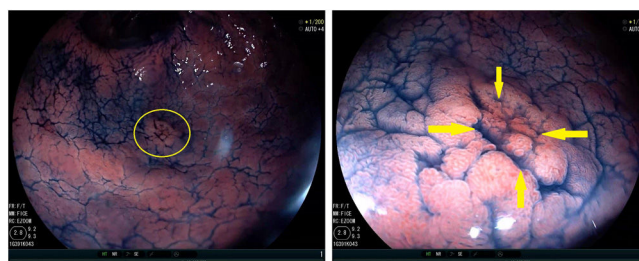


Figure 1 Antral early gastric cancer measuring 11×9 mm (yellow circle) in distant view. Chromoendoscopy with indigo carmine (left). In near view, the irregularity of the superficial glandular pattern inside the demarcation line can be seen clearly (yellow arrows) (right).

and the normal mucosa.¹⁵ These findings regarding the use of biCE have been confirmed in subsequent publications. Lee et al.¹⁶ obtained better demarcation of the margins with AA + IC compared to WLE (84% vs 67%). In particular, among the lesions with less well-defined borders, the biCE improved visualisation in 66% of cases. In this study, undifferentiated histology was the only risk factor associated with a lack of improvement in AA + IC margin detection.

Fig. 1 shows an example of demarcation of the margins of EGC with IC.

Digital chromoendoscopy

As we have seen, although there is evidence supporting the use of conventional CE in detecting GCPL and EGC, it is not without drawbacks. It is deposited in inclined areas, interfering with proper visualisation of some regions, and it slightly increases the duration of the procedure. For that reason, the different digital CE techniques are increasingly used in these indications. Of the different existing modalities, the most information is available about the NBI, blue laser imaging (BLI) and linked colour imaging (LCI) systems.

Digital chromoendoscopy in the detection of precursor lesions

Narrow band imaging

A prospective, randomised, multicentre study by Ang et al.¹⁷ compared HD-WLE to NBI for detecting focal lesions in the gastric mucosa. A total of 579 patients were randomised and endoscopy was performed with HD-WLE in 286 and with NBI in 293. The sensitivity of the NBI was clearly higher than that of the HD-WLE in detecting IM (92.3% vs 59.1%), with very similar specificity values (94.3% vs 98.6%).

As it is essential to characterise lesions and classify them adequately with digital CE techniques, Pimentel-Nunes et al.¹⁸ carried out a multicentre validation of an NBI-based classification for GCPL and EGC. Categories based on the mucosal and vascular pattern were used to establish the diagnoses of normal mucosa, IM, *Helicobacter pylori* infection and dysplasia. A high degree of repeatability was seen in the identification of the different mucosal and vascular patterns with HD-NBI and low-power magnification. The finding of tubulovillous mucosa had high diagnostic accuracy for diagnosing IM (accuracy: 84%). Images of mucosa with

irregular structure along with an irregular vascular pattern was very precise (95%) for diagnosing dysplasia. The normal mucosal pattern was associated with an absence of pathological findings in the histology study, with an accuracy of 83%.

In response to the fact that GCPL is often difficult to diagnose with WLE and the histological mapping proposed by the updated Sydney protocol may fail to diagnose 50% of patients with IM, Buxbaum et al.¹⁹ designed a study to compare the ability of NBI-targeted biopsies, HD-WLE-targeted biopsies and random histology specimens according to the Sydney protocol to diagnose IM. HD-WLE-targeted biopsies detected 29% of IM cases, NBI-targeted biopsies 65% and Sydney protocol biopsies 76%. There were no statistically significant differences in the ability to detect IM between NBI-targeted biopsies and random biopsies according to the Sydney protocol. The combination of NBI and mapping protocol detected all cases of IM, as well as 95% of the lesion locations in the gastric chamber; 9% of the areas with IM were only detected by taking biopsies. By locations, the NBI detected more IM zones in the antrum, and the mapping, in the body and incisura. When NBI was used to target sample collection, the number of biopsies needed to diagnose a patient with IM was 14.7, compared to the 21.5 needed with the mapping protocol. In this study, moreover, both NBI-targeted biopsies and mapping detected twice as many cases of IM as HD-WLE. However, even targeting biopsy taking with NBI, it was found that as many as 29% of the patients with IM would not have been diagnosed. The ideal combination for the diagnosis of IM would therefore include taking NBI-targeted biopsies and the conventional mapping proposed by the Sydney protocol.

Other studies have compared NBI and HD-WLE imaging in terms of their ability to diagnose the presence of extensive IM (affecting the body and antrum). Lage et al.²⁰ demonstrated that the accuracy for diagnosing extensive IM with HD-WLE was only 47%. However, this increased to 75% using NBI and near focus. However, the use of NBI correlated poorly with the Operative Link on Gastric Intestinal Metaplasia (OLGIM) histological classification. Even in that situation, 90% of the patients would be correctly assigned to undergo endoscopic follow-up, and over 95% to the recommendation not to continue with follow-up.

With the aim of making the diagnosis of IM with NBI more reproducible, a prospective multicentre study⁵ proposed an endoscopic classification called Endoscopic Grading of Gastric Intestinal Metaplasia (EGGIM), which scores the presence or absence of IM in five different areas of the mucosa (lesser and greater curvature of the antrum, incisura and both curvatures of the body) as: not present (0 points); focal, with involvement of $\leq 30\%$ of the surface area (1 point); or diffuse, affecting $>30\%$ of the mucosa (2 points). The scoring system gives a score ranging from 0 (normal without areas of IM) to 10 (extensive IM in all areas of the gastric mucosa) (Table 1). The diagnostic accuracy went from 83% with HD-WLE to 94% with NBI. The sensitivity for the diagnosis of IM also increased with the use of NBI from 53% to 87%, with similar specificity (98% for HD-WLE and 97% with NBI). For the detection of dysplasia, the sensitivity rose from 74% to 92%, with high specificity, regardless of the imaging technique used (99% in both). The additional benefit of NBI in the diagnosis of IM was greater in

advanced stages (OLGIM III/IV) and the diagnostic validity of the EGGIM scoring system for the presence of extensive IM defined by the AUROC value was 0.98. The use of NBI had a high degree of concordance with the histological diagnosis compared to HD-WLE. In this study, the optimal cut-off point for recommending follow-up, based on diagnostic accuracy in detecting extensive IM (OLGIM III/IV), was an EGGIM of 5 points. This endoscopic classification was validated in a multicentre prospective study by the same group²¹ in which they found that no EGGIM 0 had OLGIM III/IV lesions. Only 10.6% of EGGIM 1–4 had OLGIM III/IV, while 89.4% of EGGIM >4 had OLGIM III/IV lesions. The presence of *H. pylori* infection in this study did not affect the diagnostic accuracy of the EGGIM classification, but the presence of foveolar hyperplasia did, being associated with overestimating the existence of IM.

Blue laser imaging

The capacity of the BLI-bright mode (a variant of the BLI which improves visibility when viewing distant targets) for the diagnosis of IM was also analysed by Castro et al.²² in a prospective, single-centre, single-blind study with a cohort of 47 patients. They included the entire spectrum of gastric changes (OLGIM 0–IV) which had previously been staged endoscopically (with CE NBI and according to the EGGIM classification) and histologically (with the OLGIM classification). The diagnostic capacity of the BLI-bright mode in the diagnosis and staging of IM was assessed. The BLI-bright mode was found to be as accurate as NBI for classifying the mucosal pattern; there was 84% agreement in the EGGIM intervals (<5 , ≥ 5) with respect to the previous diagnosis with NBI, and the area under the curve for the diagnosis of OLGIM stages III–IV was 90% (sensitivity 100%, specificity 79%, positive predictive value 72% and negative predictive value 100%).

The diagnostic capacity of the BLI mode combined with AA in diagnosing IM has also been assessed. A single-centre, non-randomised study with 106 patients compared the diagnostic accuracy of HD-WLE for detecting IM to that of BLI and the combination of BLI and 0.6% AA.²³ The BLI-AA mode produced the best results (sensitivity 80.4%, specificity 90.9%), with an IM detection rate of 77.8% compared to 53.8% with BLI and 40.4% with HD-WLE.

Linked colour imaging

With regard to the diagnosis of premalignant lesions with the LCI mode (a system which enhances the contrast between the range of reds and whites), a prospective observational study compared the diagnostic capacity of WLE to LCI for detecting areas with IM.²⁴ These areas appear lavender with LCI, whereas they show up as minimal whitish elevations with WLE. The sensitivity of LCI was greater than that of WLE, with similar specificity and greater diagnostic accuracy (19% vs 91.4%; 98.6% vs 87.1%; and 62.5% vs 89.1% respectively).

In another prospective, single-blind, tandem, two-centre study in Singapore (an area with a low-risk population for gastric cancer), 90 patients were randomised to have white-light gastroscopy followed by LCI (by two different endoscopists) or vice versa.²⁵ The detection rates for atrophic gastritis and IM were higher with LCI than with

Table 1 Scoring for the *Endoscopic Grading of Gastric Intestinal Metaplasia* (EGGIM).

	Antrum		Incisura	Body	
	Lesser curvature	Greater curvature		Lesser curvature	Lesser curvature
No IM	0	0	0	0	0
≤30% IM	1	1	1	1	1
>30% IM	2	2	2	2	2

white light (2.2% vs 0.5% and 19.7% vs 7.7% respectively). The sensitivity of the LCI was greater than that of the HD-WLE, both in diagnosing atrophic gastritis (88.9% vs 22.2%) and IM (84.7% vs 32.9%), while the specificity of the two techniques was comparable.

Digital chromoendoscopy and magnification in the detection of early gastric cancer

Narrow band imaging

With regard to the detection of EGC, in the aforementioned study by Ang et al.¹⁷ the sensitivity of NBI was clearly superior to that of HD-WLE in detecting malignancy (100% vs 28.6%), with very similar specificity values (80.9% vs 78.9%). However, despite the greater sensitivity, no more EGC cases were detected in the NBI group: 3/293 patients (1%) in the NBI group and 7/286 (2.4%) in the HD-WLE group ($p=0.19$). In another multicentre, randomised, tandem study, gastroscopy was performed on a total of 4523 patients at increased risk of gastric cancer in a high-incidence area, with the aim of assessing whether the NBI mode detected a greater number of EGC than the WLE.²⁶ The detection rate with WLE was 1.9% (44/2258 patients) and with NBI 2.3% (53/2265), with no statistically significant differences between the two methods ($p=0.41$). There were also no statistically significant differences in the number of EGC not detected when the first examination was performed with white light (27.5%) or with NBI (22.4%). Sensitivity and specificity for detecting EGC were 80% and 88% respectively with WLE, and 76.8% and 91% with NBI.

In terms of characterisation, the presence of an irregular microvascular and superficial mucosal pattern with NBI was also associated with high accuracy in cancer diagnosis in a systematic review which sought to evaluate the results of NBI, flexible spectral imaging colour enhancement (FICE), and i-Scan for diagnosis of EGC and GCPL.²⁷ Thirty-one studies with NBI and seven with FICE were included. None of the publications with i-Scan met the inclusion criteria, and the data on FICE were insufficient to draw any conclusions. Ninety per cent of the studies with NBI included the use of magnification. The results with NBI for diagnosing the normal mucosal pattern showed 67% sensitivity and 81% specificity. For IM, the sensitivity was 86% and the specificity 77%, while for detecting dysplasia or cancer, the sensitivity was 90% and the specificity 83%.

Application of the vessels plus surface (VS) classification described by Yao et al.²⁸ when using NBI along with magnification endoscopy makes it possible to characterise and determine EGC with high precision. This classification is

based on the presence of a demarcated area in conjunction with an irregular microvascular and/or mucosal pattern.

The use of magnification with NBI (M-NBI) in the diagnosis of EGC has been assessed in two meta-analyses reviewed below. The one published by Hu et al.²⁹ included 14 studies with a total of 2171 patients. In half of the studies, the diagnostic criterion used to identify EGC was the VS classification. In six of them the results were compared with HD-WLE. The overall quality of the studies was considered excellent. Although marked heterogeneity in sensitivity and specificity was detected, the use of M-NBI to diagnose EGC showed values of 86% and 96% respectively, with an AUROC accuracy of 96%. In the case of the WLE, all these parameters were significantly lower, 56%, 79% and 66% respectively. It was also found that the diagnostic performance of the M-NBI was negatively influenced by the depressed lesion morphology and size <10 mm. The Zhang et al.³⁰ meta-analysis included 10 publications with 1724 patients and 2153 lesions, in which the diagnostic efficacy of M-NBI imaging was compared with WLE. Sensitivity, specificity and AUROC for M-NBI were 83%, 96% and 0.96 respectively. In the four studies assessing the diagnostic efficacy of WLE for EGC, it showed poor performance, with a sensitivity of only 48%, a specificity of 67% and an AUROC value of 62%.

The ability to determine the margins of the EGC with M-NBI has also been studied in comparison with conventional CE with IC (mode initially used for this purpose). In a multicentre, randomised study by Nagahama et al.³¹ with 384 patients, no statistically significant differences were found in the correct delineation of the margins; 85.7% with CE with IC and 88% with NBI ($p=0.63$). The two techniques therefore seem to be comparable.

Blue laser imaging

The ability of the BLI-bright mode to detect EGC was assessed in a prospective, randomised, controlled study with a back-to-back design.³² They included 298 patients in each of the two arms of the study (baseline BLI then WLE vs baseline WLE then BLI). The patients were under follow-up after a previous diagnosis of atrophic gastritis with IM or previous endoscopic resection of EGC. Real-time EGC detection was statistically significantly higher in the group whose examination began activating the BLI system (93% vs 50%).

In another study, this time prospective and multicentre, with a non-inferiority design,³³ 104 gastric cancers were evaluated prior to scheduling endoscopic submucosal dissection (ESD), with three technologies: M-BLI, M-BLI-bright and M-NBI. The VS classification was used to study the lesions. Two different examinations within a month of each other were carried out and the images taken in these procedures

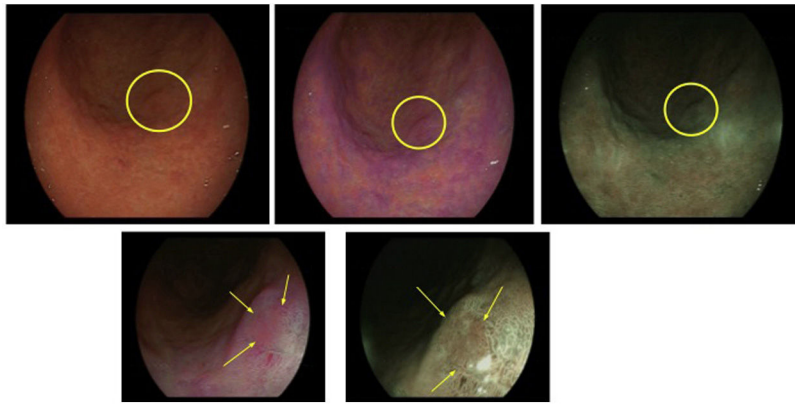


Figure 2 Early gastric cancer with histology in biopsies of low-grade dysplasia in the greater curvature of the antrum. A) High definition white light image. B) Purplish colour in LCI image. C) BLI image. D) LCI image with magnification. E) BLI image with magnification. In D and E, a peripheral demarcation line and distortion of the superficial and microvascular pattern inside it can be seen.

were assessed by a group of experts. An irregular surface pattern was found to be more easily visible with BLI modes than with NBI: 97.1% with M-BLI; 90.4% with M-BLI-bright, and 78.8% with M-NBI ($p < 0.001$). In the moderately differentiated histology subtype of adenocarcinomas, the irregular surface pattern was seen more often in M-BLI modes than in M-NBI modes (35% vs 9.9%; $p = 0.002$).

The BLI mode's diagnostic ability in detecting gastric cancer and precancerous lesions was compared with that of NBI in a meta-analysis by Zhou et al.,³⁴ which included 28 studies, with a total of 7581 patients. Virtually all of the studies were Asian, the majority (22) were with NBI and only six with BLI. The two techniques were highly accurate in the diagnosis of gastric cancer (BLI: 89% sensitivity and 92% specificity; NBI: 83% sensitivity and 95% specificity) and in the diagnosis of precancerous lesions (BLI: 81% sensitivity, 90% specificity; NBI: 80% sensitivity, 88% specificity), with no statistically significant differences. However, the statistical analysis showed high heterogeneity, none of the studies with BLI were of very high quality, and none directly compared the two techniques.

Another recent meta-analysis compared endoscopy with magnification, alone or in conjunction with different digital CE techniques (NBI, BLI), to HD-WLE in the diagnosis of EGC.³⁵ Eight prospective studies were included, with a total of 5731 lesions. Magnification endoscopy showed greater diagnostic accuracy than conventional white light endoscopy in detecting EGC (OR: 2.97). Compared to HD-WLE, diagnostic accuracy was higher when combined with white light magnification (OR: 1.43) and even higher with NBI magnification (OR: 2.56) and with BLI magnification (OR: 3.13). There were no significant differences between M-NBI and M-BLI.

Linked colour imaging

Gao et al.³⁶ compared the LCI mode with conventional white-light endoscopy for the detection of EGC. In this prospective, multicentre study, 2382 randomised patients underwent gastroscopy with white light or with white light and LCI, with biopsies taken from suspicious lesions, histology being the gold standard. EGC detection was superior

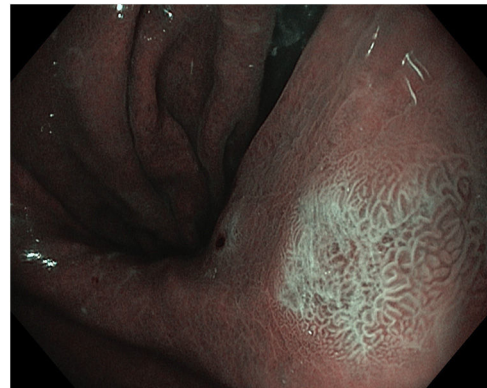


Figure 3 Focus of intestinal metaplasia (IM) close to the incisura, M-NBI image. The light blue crest images can be seen clearly.

with the LCI mode, with a diagnostic OR of 1.93 (95% CI: 1.36–2.74).

The detection of gastric cancer with LCI was also assessed by Yamaoka et al.³⁷ in a prospective, single-centre study in Japan, in which 500 patients under follow-up for atrophic gastritis had an endoscopy, first examining the gastric cavity with white light, followed by LCI mode and finally with BLI-bright. A total of 16 gastric cancers (13 EGC and 3 adenomas) were detected, 25% of which were not visible with white light but were visible with the LCI mode (3 EGC and 1 adenoma). The lesions visible with LCI were smaller compared to those initially diagnosed with white light (mean diameter 7.7 mm vs 21.2 mm). No lesions were diagnosed solely with the BLI-bright mode having previously been invisible with the other techniques. Yoshifuku et al.³⁸ evaluated the visibility of the EGC with BLI, LCI and WLE. To do this they carried out a retrospective analysis based on the still images of the lesions under study. The visibility of 73% of the lesions improved with LCI, but only 24% with BLI-bright. The use of LCI did not seem to worsen the visibility of the EGC in any of the cases.

Table 2 Gastric cancer precursor lesions: summary of the main studies.

Study; year	Asian (yes/no)	Design	Patients, n	IM results					
Song et al.; 2017	Yes	Prospective Single-centre Not randomised	105						
Ang et al.; 2015	Mixed	Prospective Multicentre Randomised	579	S 77%	NBI		Sp 94%	HD-WLE	
Pimentel-Nunes et al.; 2012	No	Retrospective Two-centre Not randomised	85	S 92.3%	Sp 94.3%		S 59.1%	Sp 98.6% NBI-M (×1.5)	
Buxbaum et al.; 2017	No	Prospective Single-centre Not randomised	112	Tubulovillous pattern S 89%	NBI	Sp 90%	HD-WLE	Light blue crest sign S 48%	Sp 96% Mapping biopsies
Lage et al., 2015	No	Single-centre Not randomised	35	S 65%	Light-NBI	S 29%	S 76% HD-WLE	NBI-NF-M (×1.5)	
Esposito et al.; 2019	No	Multicentre Prospective Not randomised	250	S 63%	S 60%		S 73%	NBI EGGIM > 4 (diagnosis of OLGIM III/IV)	
Sha et al.; 2017	Yes	Single-centre Prospective Not randomised	132	S 89.4%	NBI-AA	NBI		Sp 94.6%	WLE
				S 87.9%	Sp 68.2%	S 66.7%	Sp 68.2%	S 33.3%	Sp 28.8%

Table 2 (Continued)

Study; year	Asian (yes/no)	Design	Patients, n	IM results							
				BLI-AA				BLI		WLE	
Chen et al.; 2019	Yes	Prospective Single-centre Not randomised	106								
Castro et al.; 2019	No	Prospective Single-centre Not randomised	37	S 85.4%	Sp 84.6%	S 68.3%	Sp 69.2%	S 41.5%		Sp 38.5%	IM (EGGIM $\geq$ 5)
Ono et al.; 2018	Yes	Prospective Single-centre Not randomised	128	BLI-bright S 100%			NBI Sp 79%				WLE
						LCI					
Wu et al.; 2021	Yes	Prospective Two-centre Tandem	90	S 91.4%	Sp 81.7%		S 19%			Sp 98.6%	WLE
						LCI					
Kikuste et al.; 2013	Mixed	Systematic review	31 studies	S 84.7%	Sp 92.2%		S 32.9%			Sp 97.2%	
				NBI-M							
Rodríguez-Carrasco et al.; 2020	Mixed (mostly Asian)	Meta-analysis	10,175	S 86%				Sp 77%			
				NBI		FICE-M		BLI		LCI	
Zhou et al.; 2020	Yes	Meta-analysis	7581	S 84%	Sp 95%	S 96%	Sp 80%	S 78%	Sp 83%	S 73%	Sp 92%
				NBI				BLI			
				S 80%		Sp 88%		S 81%		Sp 90%	

AA: acetic acid; HD-WLE: high definition white light endoscopy; M: magnification; NF: near focus, S: sensitivity; Sp: specificity.

Study; year	Asian (yes/no)	Design	Patients, n	Results									
				Dysplasia and/or EGC									
Ang et al.; 2015	Mixed	Prospective Multicentre Randomised	579	NBI					HD-WLE				
				S 100%	Sp 80.9%			S 28.6%			Sp 78.9%		
Pimentel- Nunes et al.; 2012	No	Retrospective Two-centre Not randomised	85						NBI-M (×1.5)				
				S 96%				Sp 98%					
Yoshifuku et al.; 2017	Yes	Retrospective Single-centre Not randomised	82	LCI					BLI- <i>bright</i>				
				Improves visibility 73%					Improves visibility 20%				
Dohi et al.; 2019	Yes	Prospective Two-centre Randomised (<i>back to back</i>)	629	BLI- <i>bright</i>					HD-WLE				
				S 93%				S 50%					
Dohi et al.; 2017	Yes	Prospective Multicentre Not randomised	104	DL		Irregular MSP			Irregular MVP				
				BLI-M 96%	BLI- <i>bright</i> -M 98%	NBI-M 98%	BLI-M 97%	BLI- <i>bright</i> -M 90%	NBI-M 79%	BLI-M 95%	BLI- <i>bright</i> -M 95%	NBI-M 96%	

Table 3 (Continued)

Study; year	Asian (yes/no)	Design	Patients, n	Results			
				Dysplasia and/or EGC			
Gao et al.; 2021	Yes	Prospective Single-centre Randomised	2382		HD-WLE		HD-WLE + LCI
Yamaoka et al.; 2020	Yes	Prospective Single-centre Not randomised	500	Detection rate 4.3% 1st WLE		Detection rate 8% 2nd LCI	3rd BLI- <i>bright</i>
Kikuste et al.; 2013	Mixed	Systematic review	31 studies	S 75% NBI-M S 90%	S 100%		S 100%
Hu et al.; 2015	Yes	Meta- analysis	2171	NBI-M S 86%	Sp 96%	HD-WLE S 57%	Sp 79%
Zhang et al.; 2016	Yes	Meta- analysis	1724	NBI-M S 83%	Sp 96%	HD-WLE S 48%	Sp 67%
Rodríguez-Carrasco et al.; 2020	Mixed (mostly Asian)	Meta- analysis	19 studies	NBI S 87%		Sp 97%	
Zhou et al.; 2020	Yes	Meta- analysis	7581	NBI S 83%	Sp 88%	BLI S 89%	Sp 92%
Le et al.; 2021	Yes	Meta- analysis	5731	Diagnosis compared with WLE-M DOR 2.97	HD-WLE NBI-M DOR 2.56	BLI-M DOR 3.13	

DL: demarcation line; DOR: diagnostic odds ratio; EGC: early gastric cancer; HD-WLE: high definition white light endoscopy; M: magnification; MSP: microsurface pattern; MVP: microvascular pattern; S: sensitivity; Sp: specificity.

Fig. 2 shows the endoscopic characteristics of malignant lesions with each of the different modalities we have described.

Rodríguez-Carrasco et al. recently published a meta-analysis³⁹ on the use of advanced imaging techniques in the diagnosis of precancerous gastric lesions. They included a total of 44 studies and 10,451 biopsied areas. Most of the studies included were by groups in the Far East and had a prospective design. White light was generally used before CE and magnification. White light was compared to digital CE in 25 of the studies, and with different CE techniques in another seven. The gold standard in all of them was the histological study.

With regard to NBI, 30 studies which included 8482 patients were analysed. For the diagnosis of IM, in the analysis by biopsy the sensitivity was 84% and the specificity 95%, with high heterogeneity. When magnification was used, the presence of the light blue crest (LBC) sign as the only marker for IM had low specificity compared to the use of other markers (tubulovillous pattern, opaque white substance and marginal turbid band) or a combination of these (89% vs 96%). In the studies without magnification, diagnostic accuracy was significantly higher in those using the tubulovillous pattern, with or without LBC. The sensitivity and specificity of this finding were 88% and 97% respectively. Fig. 3 shows the endoscopic appearance of IM with magnification and NBI (M-NBI).

The meta-analysis included three studies which analysed BLI, with 736 patients. In the diagnosis of IM, a sensitivity of 78% and a specificity of 83% were obtained. Without magnification, however, sensitivity and specificity were lower (68% and 69% respectively). The studies with magnification obtained a diagnostic accuracy identical to that achieved with NBI.

With LCI, there were two studies with 176 patients. For the diagnosis of IM, the sensitivity was 73% and the specificity 92%.

For the diagnosis of dysplasia and EGC, results were only obtained with NBI. In the biopsy analysis, the sensitivity and specificity with NBI were 87% and 97% respectively, with high heterogeneity. The specificity was significantly higher in the group which used magnification (97% vs 84%). Also in the studies with magnification, the specificity was higher in the subgroup that used the VS classification (98% vs 94%), although with lower sensitivity (86% vs 94%). Depressed morphology increased diagnostic accuracy (88% sensitivity, 96% specificity).

The results of the main studies with regard to gastric cancer precursor lesions are summarised in Table 2. The results on the diagnosis of dysplasia and EGC are summarised in Table 3.

Conclusions

Endoscopy is the main tool for detecting GCPL and EGC. However, its diagnostic ability could be improved, particularly with the exclusive use of white light endoscopy, and all the more with high definition. These results improve with the use of CE and magnification.

More widespread use of advanced imaging techniques can be achieved with adequate training in this area. Recent stud-

ies suggest that it may be enough to have online training with suitable feedback.^{40,41}

For the detection and characterisation of IM, the routine use of conventional or digital CE is recommended, as both have been shown to improve diagnostic accuracy. In the case of the different modalities of digital CE, NBI is the most widely studied, and mucosal patterns (tubulovillous pattern, LBC sign) and scales (EGGIM) predicting both the existence of IM and its extension have been designed and validated. The new modalities of digital CE (BLI and LCI) achieve results comparable to NBI, although more robust studies are still needed to confirm these findings.

For EGC, the use of advanced imaging techniques has not been shown to increase the number of lesions detected. Both conventional and digital CE improve the demarcation of the EGC margins. With regard to the different digital CE techniques, their sensitivity for adequately characterising these lesions seems to be higher than that obtained with HD-WLE. There is sufficient evidence to recommend the use of magnification and VS classification with CE techniques for characterising these lesions.

In short, the evidence in favour of using advanced imaging techniques in the detection and follow-up of GCPL and EGC supports the recommendations recently made by various scientific societies here in Spain.²

Funding

There was no funding for this article.

Conflicts of interest

Maria Moreno-Sanchez, Gloria Fernández Esparrach and Joaquín Cubiella state that they have no conflicts of interest.

Jose Carlos Marin-Gabriel has received fees from Fujifilm for giving a lecture.

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