World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i10.472

World J Gastrointest Endosc 2012 October 16; 4(10): 472-478
ISSN 1948-5190 (online)
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MINIREVIEWS

Role of digital chromoendoscopy and confocal laser endomicroscopy for gastric intestinal metaplasia and cancer surveillance

Rapat Pittayanon, Rungsun Rerknimitr

Rapat Pittayanon, Rungsun Rerknimitr, Division of Gastroenterology, Department of Medicine, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand
Author contributions: Pittayanon R and Reknimitr R contributed equally to the article selection and manuscript's writing.
Correspondence to: Rungsun Reknimitr, MD, Professor, Division of Gastroenterology, Department of Medicine, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand. ercp@live.com
Telephone: +66-2-2564356 Fax: +66-2-2527839
Received: November 15, 2011 Revised: August 1, 2012
Accepted: October 13, 2012
Published online: October 16, 2012

Abstract

In Japan and countries such as South Korea and Taiwan, China, the standard technique for detecting early gastric cancer (EGC) is chromoendoscopy. This technique involves a magnified endoscope and the use of an indigo-carmine spray to distinguish between EGC and non-EGC areas. However, this technique is not widely adopted in many parts of the world. One important reason for limited use is that this technique needs an experienced endoscopist to interpret the images during the procedure. In addition, the sensitivity for detecting gastric intestinal metaplasia (GIM), a precancerous lesion of EGC, is graded as suboptimal. Moreover, the requirement of a cumbersome spraying method is inconvenient and needs preparation time. Easier digital chromoendoscopy techniques, such as Narrow-band Imaging and Flexible spectral Imaging Color Enhancement, have been reported to facilitate targeted GIM and EGC biopsy. They provide higher sensitivities over conventional white light endoscopy. Recently, the novel technology of confocal laser endomicroscopy has been introduced as a high-magnification (1000 ×) real-time evaluation for many early gastrointestinal (GI) cancers and precancerous GI lesions, including colonic polyp, Barrett's esophagus, and GIM. The advantage of this technique is that it can be used as an *in vivo* confirmation of the presence of GIM and EGC during endoscopic surveillance. This review aims to explain the current information on the usefulness of digital chromoendoscopy and confocal laser endomicroscopy for evaluating GIM and EGC during endoscopic surveillance and the possible future role of these techniques for GI cancer screening programs.

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Key words: Confocal laser endomicroscope; Chromoendoscopy; Gastric intestinal metaplasia; Gastric intestinal metaplasia

Peer reviewers: Elias Xirouchakis, MD, GI and Hepatology Department, Athens Medical, P. Falirou Hospital, Areos 36, P. Faliro, PC 175 62, Greece; Cristina Trovato, MD, Division of Endoscopy, European Institute of Oncology, Via Ripamonti, 435-20141 Milano, Italy

Pittayanon R, Rerknimitr R. Role of digital chromoendoscopy and confocal laser endomicroscopy for gastric intestinal metaplasia and cancer surveillance. *World J Gastrointest Endosc* 2012; 4(10): 472-478 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i10/472.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i10.472

INTRODUCTION

Gastric cancer remains the second leading cause of cancer-related deaths in the world. The incidence of gastric cancer is predominant in East Asia[1]. Usually, patients with early gastric cancer (EGC) are asymptomatic, whereas advanced stage patients typically present with bleeding, vomiting, and weight loss and have a dismal prognosis. Although curative surgery is recommended in all patients

with possible resectable lesions, the loss of gastric accommodation is an expected morbidity. There are some patients with EGC who do not require a full-thickness resection by surgery; endoscopic resection, which has less morbidity, is the preferred treatment for these individuals.

The pathogenesis of intestinal type gastric cancer is a sequential multistep pathway, starting with a precancerous lesion such as a gastric intestinal metaplasia (GIM) before developing into EGC and then growing into a full blown carcinoma[2] (Figure 1). Therefore, strategies that can detect precancerous lesions and monitor them before they become more significant cancers are very beneficial. Led by Japanese endoscopists, over the last three decades the tools for EGC detection have progressed from gastro cameras to magnifying chromoendoscopy. Subsequently, a one-button-touch technique called digital chromoendoscopy (DC), including Narrow-band Imaging (NBI) and other optimal band imaging, was promoted as a useful instrument for detecting many GI precancerous lesions, such as colonic adenoma, Barrett's esophagus, and GIM[3-9]. Recently, a confocal laser endoscopy (CLE) technique that provides a higher magnification (× 1000) of the GI tract epithelium has been used by many investigators as a tool for real-time GIM and EGC confirmation[10-13]. Moreover, CLE can be applied at the gastric lesion as a confirmation tool of tumor margin during, before, and after endoscopic treatment[14,15]. In this review, we present the techniques and the possible roles of DC and CLE for GIM and gastric cancer surveillance. Future improvements for technology and a possible protocol are also provided.

THE HISTORY OF GASTRIC CANCER SURVEILLANCE BY ENDOSCOPY

According to the Correa pathway[2], atrophic gastritis, GIM and dysplasia are premalignant stages of gastric cancer. To date, there have been many technologies developed to detect these precancerous lesions. After the first debut of the gastro-camera in 1962[16,17], Nakayama[18] published a pioneering study of gastric cancer detection with a gastro-camera in 1969. However, the sensitivity and standardization of gastro-cameras for EGC detection were very limited. Subsequently, conventional white light endoscopy (WLE) replaced the use of gastro-cameras in 1984[19]. Unfortunately, the sensitivity of WLE for abnormal gastric epithelial detection was suboptimal (less than fifty percent)[3,6,19]. Later, a more sensitive technique called chromoendoscopy was developed to improve the detection of EGC. This technique was developed by pioneering Japanese endoscopists. It involves the use of a dye spray and a magnified endoscope. The sensitivity for EGC diagnosis was reported to be excellent (98%) with this technique[20,21]. Currently, this technique has been widely adopted as the standard practice in Japan, South Korea, and Taiwan. Among the many premalignant conditions, GIM has been widely targeted because of its unique morphology that has a higher potential for being distinguished from other normal gastric mucosa.

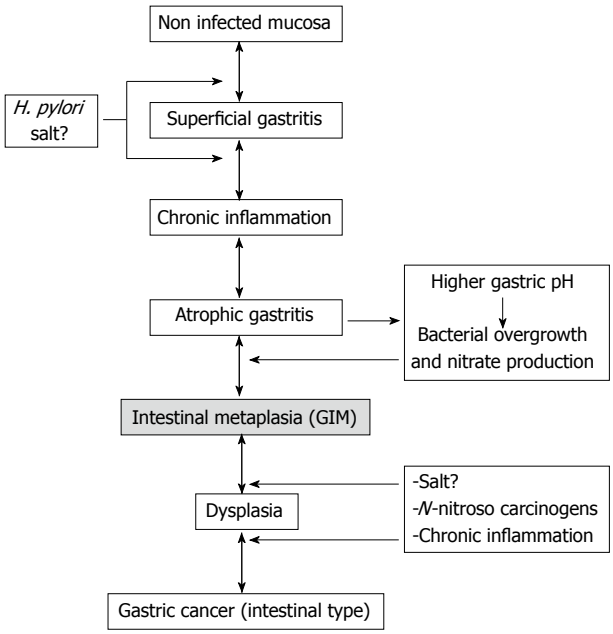

Figure 1 Multistep pathway in the pathogenesis of intestinal-type gastric cancer (Correa pathway).

For instance, methylene blue magnified chromoendoscopy provides a fair sensitivity (76%) for confirming a diagnosis of GIM by identifying blue irregular marks, blue round pits, tubular pits, blue villi, and blue small pits[22]. Therefore, the natural dye spraying method is not popular worldwide because it provides suboptimal accuracy for GIM diagnosis. New methods such as NBI and optimal band imaging or the more accurate confocal laser endomicroscopy (CLE) are needed to more easily improve findings. Vascular patterns and image analysis are easier and better detected with these new methods. For instance, Narrow Band Imaging with magnifying endoscopy (NBI/ME) has shown better sensitivity (90%), and CLE has been reported to provide the best sensitivity for confirming a diagnosis of GIM (98%, Table 1).

DIGITAL CHROMOENDOSCOPES

Currently, there are three commercially available DC systems: Flexible Spectral Imaging Color Enhancement or Fuji Intelligent Color Enhancement (FICE; Fujifilm Corporation, Tokyo, Japan), I-Scan Pentax (Hoya Corporation, Tokyo, Japan), and NBI (Olympus Corporation, Tokyo, Japan). All of these systems provide a real-time image enhanced video stream. FICE and I-Scan rely on post-processing reconstruction of the images captured from white light by selecting only the optimal wavelengths of the three colors (red, green, and blue) in the 400-550 nm range. This in turn enhances the contrast of the captured images[23]. In contrast, NBI relies on a filter that selects only blue and green lights, each delivering a relatively narrow bandwidth that is preferably absorbed by hemoglobin. This in turn enhances areas with hypervascularity such as neoplasms and inflamed mucosa[24].

There have been two published articles on the use of

Table 1 Sensitivities of different endoscopic technologies for gastric intestinal metaplasia detection

Endoscopy in GIM	Ref.	Sensitivity (%)
White light endoscopy	Sauerbruch *et al*[19]	< 50
Digital chromoendoscopy (NBI)	Capelle *et al*[5]	71
Methylene blue magnified chromoendoscopy	Dinis-Ribeiro *et al*[22]	76
Digital magnified chromoendoscopy (Non-sequential-NBI)	Rerknimitr *et al*[7]	91
Digital magnified chromoendoscopy (sequential-NBI)	Uedo *et al*[4]	89
Endoscopic-based confocal laser endomicroscopy	Guo *et al*[40]	98

GIM: Gastric intestinal metaplasia; NBI: Narrow-band Imaging.

FICE for EGC detection. Without magnification, Mouri and colleagues showed a 46 % improvement in image quality after applying the FICE system in patients in whom EGC was suspected[25]. However, to characterize the details of the mucosal structure, magnification of the images was required. FICE with a × 20 to × 30 magnification can help to characterize an upper GI tract polypoid lesion by detailing abnormal capillary architecture and pit pattern[23]. For a non-polypoid lesion, FICE can assist in the delineation of abnormal from normal mucosa and can ensure a complete endoscopic resection. A pioneering study of NBI for EGC detection was reported by Yao *et al*[24]. They proposed criteria for EGC diagnosis with NBI/ME and reported their validity in their cohorts with the negative and positive predictive values as 100% and 93%, respectively[26]. Following that study, there have been many reports of the usefulness of NBI for EGC detection. For instance, in 2010, Ezoe *et al*[3] published the diagnostic accuracy of NBI/ME for EGC diagnosis in 57 suspected depressed-EGC lesions. The study concluded that by adding NBI/ME to WLE, NBI/ME significantly increased the accuracy and sensitivity for EGC diagnosis from 44% to 79% and from 33% to 70%, respectively[3]. Later, Kato *et al*[6] used triad-based diagnosis [(1) the disappearance of fine mucosal structure; (2) the presence of microvascular dilation; and (3) the evidence of heterogeneity in the shape of microvessels] to diagnose EGC in 201 suspected EGC lesions in 111 patients at high risk for EGC. They found that the sensitivity and specificity of magnified NBI/ME for EGC diagnosis using these criteria were 92% and 94%, respectively, whereas the sensitivity and specificity of WLE were only 42.9% and 61.0%, respectively[6]. However, the generalization of DC for EGC screening has been challenged by many experts; therefore, the reading accuracy of all of the criteria needs to be validated in larger populations.

The current Asia-Pacific Consensus on the role of DC for the diagnosis of upper GI tract superficial neoplasia does not recommend the use of DC as the initial test because it is claimed that it is impractical to scan the whole gastric lumen with a magnified endoscope. However, they recommend using DC to distinguish malignant from non-malignant abnormal gastric lesions only after spotting the suspicious lesions with WLE. In addition, they recommend using DC to determine the extent but not the depth of EGC[27].

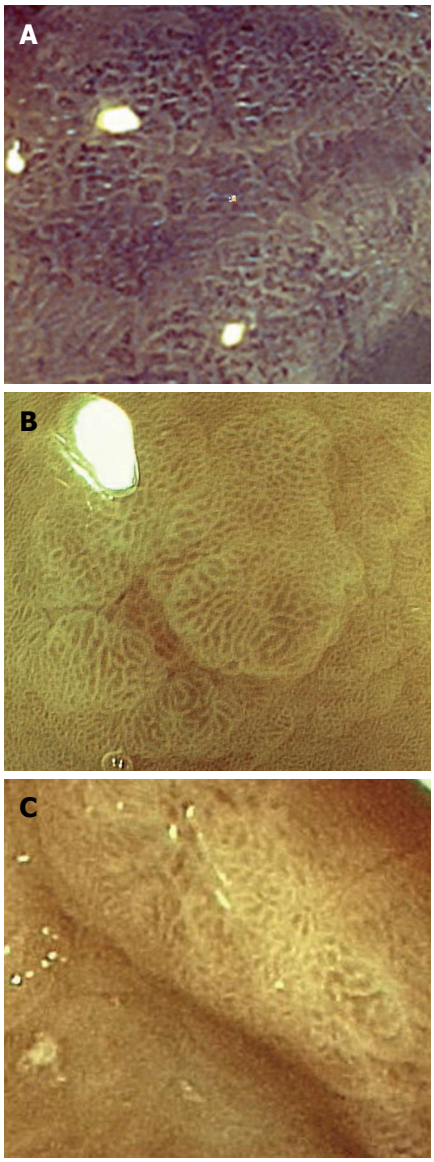

Figure 2 Pictures under flexible spectral imaging color enhancement. A: Light blue crest; B: Villous pattern; C: Large long crest.

Technically, GIM can be detected by DC due to a typical characteristic called light blue crest (LBC)[4,5,7] (Figure 2A). LBC is defined as a fine, blue-white line on the crests of the epithelial surface. LBC has the highest sensitivity for GIM detection (89%)[4]. In addition, Bansal *et al*[28] showed that the sensitivity and specificity of the ridge/villous pattern for the diagnosis of GIM were 80% and 100%, respectively; Tahara *et al*[29] reported a high sensitivity of ridge/villous pits for GIM diagnosis at 95%. Moreover, the results of other endoscopic patterns for GIM diagnosis have been studied by Rerknimitr *et al*. They added the villous pattern (VP; Figure 2B) and large long crest (LLC; Figure 2C) to improve the yield for GIM diagnosis. By using all three criteria (LBC, VP and LLC), the sensitivity for GIM diagnosis increased to 91%[7] (Ta-

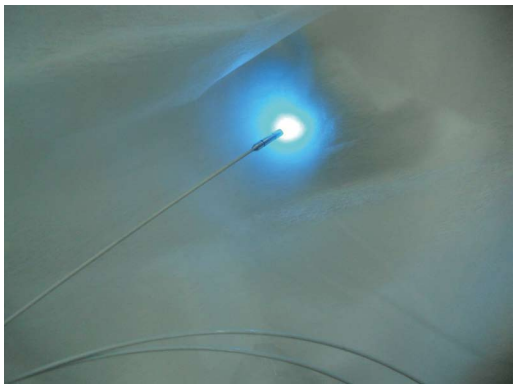

Figure 3 The probe-based confocal laser endomicroscope probe.

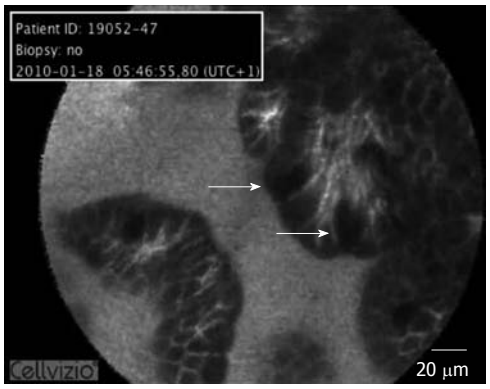

Figure 4 An image of gastric intestinal metaplasia from a probe-based confocal laser endomicroscope (mucin-containing goblet cells; arrows).

ble 1). Currently, there are more NBI/ME studies than FICE studies of GIM diagnosis by DC.

In summary, DC (FICE, I-Scan, and NBI) is a non-invasive test that provides higher sensitivities for EGC and GIM detection than WLE. DC is more convenient to use than conventional chromoendoscopy. It helps to distinguish suspicious EGC lesions and can delineate the extent of the cancer. Practically, primary screening should be performed with WLE; DC can be used after spotting suspicious lesions.

CONFOCAL LASER ENDOMICROSCOPY

CLE is the latest novel endoscopic device[30]. CLE is a refined instrument that provides high-magnification (× 1000) imaging compared to standard microscopic examination. It enables a real-time display of a 12 frames/second video stream during the endoscopic examination. In other words, it is a real-time endoscopic read for histology without the need for a biopsy[10,11,31-34]. Currently, there are two techniques: (1) endoscopic-based confocal laser endomicroscopy (eCLE; Pentax, Tokyo, Japan) and (2) probe-based confocal laser endomicroscopy (pCLE, Mauna Kea Technologies). Both require an intravenous contrast injection (fluorescein) or a topical dye spray (e.g., acriflavine hydrochloride, tetracycline, or cresyl violet) to enhance all of the vascular supplied mucosal

Table 2 Criteria for mature and immature gastric intestinal metaplasia by endoscopic-based confocal laser endomicroscope[40]

	Mature GIM	Immature GIM
Gland	Regular	Tortuous
Capillary	Regular	Irregular
Goblet cell	Regular	Regular

GIM: Gastric intestinal metaplasia.

structures[35]. eCLE is an endoscopic-based CLE that integrates a confocal fluorescence microscope into the distal tip of a conventional 12.8-mm diameter flexible videoendoscope. The other system, known as pCLE, is provided by Mauna Kea Technologies (Paris, France) and is a 2.5-mm catheter probe transported 488-nm laser beam with a scanning field of 30 000 pixels[34,35] (Figure 3). With the current technology, the eCLE imaging system provides a superior quality of confocal image over pCLE. Although eCLE shares the same wavelength (488 nm) as pCLE for detecting the fluorescence effect at 505-585 nm, eCLE also provides a Z-axis, which creates an adjustable focus at different depths. In contrast, the image from pCLE is fixed at only one depth. Therefore, different levels of histological structures can be displayed by eCLE. Another advantage is that eCLE can provide a better (0.7 μm) lateral resolution than pCLE (1 μm)[34,36]. In addition, eCLE has a field of view of 475 × 475 μm with a variable imaging plane depth of up to 250 μm, whereas the pCLE system has a fixed imaging plane at the maximum depth of 200 μm. However, pCLE is more flexible because it can be used with any endoscopes that accept 10 Fr size accessories. Moreover, the frame rate of the pCLE system is much faster (12 images/second) than the current eCLE system (± 1 image/second)[37]. Therefore, the stream of pCLE images is closer to standard video output (Table 2).

Fluorescein, which is a slightly acidic and hydrophilic dye, has been used intravenously as a staining substance. Almost immediately after injection, it can be found distributed throughout the surface of columnar epithelial cells arranged in a cobblestone pattern with round gland openings. Fluorescein enhances a real-time histological reading by staining the connective tissue matrix of lamina propria and blood vessels running in the deeper mucosa[32,38]. A standard structure that contains vessels, such as a normal gastric epithelium, can be observed as a brighter object after fluorescein injection. In contrast, any structure that has no vascular supply, such as mucin, will not be stained by fluorescein. Hence, mucin-containing goblet cells, indicating GIM, will appear dark[32]. Fluorescein is a very safe contrast agent, with less than two percent of patients developing mild side effects such as nausea/vomiting, transient hypotension without shock, injection site erythema, diffuse rash and mild epigastric pain[39].

Another agent, acriflavine hydrochloride, has been most extensively used as a topical dye. However, it only

stains the very superficial layer of the GI tract mucosa[33] and does not penetrate into the deeper mucosa. Hence, it is not currently recommended for EGC screening.

Mucin-containing goblet cells can be readily recognizable by CLE (Figure 4). The sensitivity of eCLE for GIM diagnosis is excellent at 98%[12]. In addition, eCLE can further diagnose gastric dysplasia and early malignant gastric change with a very high sensitivity at 89%-91%[10,11]. Although current CLE technology is still not optimal for distinguishing between mature (regular glands, goblet cells, and columnar mucous cells) and immature (tortuous alveolar and irregular capillaries) GIM (Table 2), eCLE may be able to do so with 68% sensitivity[40]. In addition, Li *et al*[41] revealed that the score included 3 parameters: gland architecture, cell morphology, and vessel architecture, with marks ranging from 0-3 for each parameter. If the summation of the score $\geqslant$ 5, eCLE could differentiate high-grade from low-grade dysplasia with a sensitivity and specificity of 66% and 88%, respectively[41].

Recently, Lim *et al*[42] reported the validity scores from 3 experienced and 3 inexperienced readers who read GIM on the images captured by eCLE. They found that the experienced group had greater specificity in GIM interpretation (93% *vs* 62%, $P < 0.001$). However, the reading results of *ex-vivo* gastric cancer between the two groups were not different (a sensitivity of 93% *vs* 86%, $P = 1.00$, and a specificity of 87% *vs* 80%, $P = 0.34$)[42]. Another pCLE study on the learning curve for GIM diagnosis revealed that it is possible to train beginners to read GIM after a 3-d training session. However, the reading results were not as good as the experts' readings (the sensitivities, specificities and accuracies were 96% *vs* 87%, $P = 0.03$; 95% *vs* 82%, $P = 0.03$; and 95% *vs* 84%, $P = 0.01$; respectively)[43].

Although pilot studies have reported excellent results in EGC reading[10,11], the appearance of EGC under confocal laser microscopy has not been standardized due to the difficulty in reading the non-structural mitotic glands of the stomach. *In vivo* histological diagnosis for gastric cancer was first reported as an observational study in 2006 by a Japanese group[10]. Using conventional histology as the gold standard, in this study the *ex vivo* examination of 27 gastric cancerous tissues under eCLE yielded 89% sensitivity, 100% specificity, and 94% accuracy[10]. Another study by Kitabatake *et al*[11] showed comparable results for EGC reading by eCLE (91% sensitivity, 97% specificity, and 95% accuracy). Of note, the authors excluded 40% of their images due to suboptimal quality. Because undifferentiated adenocarcinoma is not amenable to endoscopic therapy, surgery is the only option. Therefore, it is important to have a tool that accurately distinguishes between differentiated and undifferentiated adenocarcinoma like eCLE (86%-95%)[15,44]. However, because these studies were performed by the experts in CLE reading, there is no guarantee that others will duplicate the results in standard practice. Therefore, further study on the learning curve for EGC reading by CLE is required. In the authors' opinion, employing CLE for GIM diagnosis in standard practice is more promising when using the well-described findings that require only a short learning curve. In contrast, there is a need for standardization for EGC reading by CLE before it can be recommended for use in routine work.

ENDOSCOPIC TECHNIQUES FOR GIM AND EGC DIAGNOSIS

Because GIM and EGC are usually observed as diminutive lesions, a biopsy targeted by conventional WLE may be difficult. However, many synchronous GIMs or EGC lesions can be found in the stomach, and random biopsy may not be practical because it would be time consuming. Likewise, using CLE as the initial mode for screening is impractical because of its limited field of view per one examination. Therefore, we recommend using WLE (preferably with a high definition model) to identify abnormal gastric epithelium, and then to use magnified DC imaging to further characterize and perhaps identify more lesions if possible. We recommend performing a further study on the suspicious lesion with CLE by applying the scope or probe on the lesion and taking a biopsy if EGC or GIM with high grade dysplasia is suspected. In contrast, taking a biopsy from a lesion confirmed as a complete GIM by CLE may not be necessary because a complete GIM contains a very low risk for developing gastric cancer. By using this protocol, the procedure duration can be shortened. We recommend this combination of techniques because our study showed higher sensitivity (89%) and specificity (94%) for GIM diagnosis by adding pCLE on DC[43]. In addition, NBI/ME needs intensive training for GIM interpretation[45], whereas pCLE requires a shorter training session. Moreover, interobserver agreement among expert endoscopists for GIM detection based on each criterion of NBI/ME is still suboptimal ($\kappa = 0.60$ for LBC and no data for the other criteria)[45], whereas pCLE provided a better score by showing an almost perfect agreement ($\kappa = 0.83$) among experienced readers[46].

To avoid the shaking of the picture during the CLE procedure, adequate sedation is necessary in every patient because the procedure requires a very cooperative subject. A standard conscious sedation with intravenous midazolam and meperidine or propofol is recommended. Moreover, hyoscine or glucagon injection to decrease bowel movement is a requisite to ensure the stability of the examination. In addition, a simethicone solution should be rinsed to reduce mucous and gas bubbles in the stomach. Intravenously administering 10% fluorescein sodium at a dose of 2.5 mL right before the examination is adequate for a 30-min study.

A transparent cap is needed to maintain the focus distance during examination with pCLE. Slight pressure on the endoscope with the cap on is recommended to stabilize the target; once the target is identified, a biopsy can be obtained. For pCLE, a mark should be made by pressing a probe on the targeted gastric mucosa. The biopsy needs to be performed immediately after replacing the probe with a forceps into the endoscope accessory

channel. Of note, a procedure duration of longer than 20-30 min may have an impact on the image quality due to procedure-related mucosal damage and contrast leakage. The most important factor for excellent image interpretation is the experience of the endoscopist.

DC has been proven to delineate the EGC margin from non-malignant gastric mucosa[47,48]. The Asia-Pacific Consensus recommended DC as an adjunctive tool for evaluation of the EGC margin. They recommended using DC both before and after endoscopic mucosal resection or endoscopic submucosal dissection[27]. To date, there has been no study published on employing CLE to evaluate the EGC margin. In the authors' opinion, CLE may be useful for evaluating the residual malignant mucosa after endoscopic treatment. In addition, DC has been proven to be useful for GIM surveillance[49]. A group from South Korea recommended a 2-year surveillance interval in patients with GIM[50]. However, in a patient with extensive GIM, a much shorter annual surveillance with magnified DC is recommended after the resection of EGC[49].

CONCLUSION

There has been a significant evolution in the endoscopic diagnosis of GIM and EGC. The current standard practice relies on a random biopsy under WLE. Although many expert centers have put magnified chromoendoscopy into their standard protocol for EGC surveillance, this practice has not been accepted worldwide for many reasons. Magnified DC is a promising tool for overcoming this problem, and may be beneficial for targeted biopsy. As an additional asset, CLE has been proposed for real-time confirmation of GIM without the need for a biopsy. However, the use of CLE is practical only in a patient with GIM, whereas the use of CLE for EGC confirmation is limited due to poor standardization of the criteria, for which a long learning curve may be required. In conclusion, histological examination by DC targeted biopsy may be recommended as a new "gold standard" for EGC diagnosis. CLE is a better alternative over a routine randomized biopsy in GIM surveillance because it can reduce unnecessary random biopsies.

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