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ORIGINAL ARTICLE

Predictability of gastric intestinal metaplasia by patchy lavender color seen on linked color imaging endoscopy

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Abstract

We aimed to investigate the ability of linked color imaging (LCI) versus white light endoscopy (WLE) to detect gastric intestinal metaplasia (GIM). One hundred and seven participants who underwent upper gastrointestinal endoscopy were included. Under WLE endoscopy, biopsies were performed on any suspected abnormal mucosal changes. Under LCI endoscopy, we tested whether the specific color feature of patchy lavender color (PLC) pathologically indicated GIM. Biopsies were randomly performed in participants who had neither PLC nor suspected lesions. The detection abilities of LCI and WLE were assessed by comparison of histological and endoscopic findings. A total of 41 participants had histological GIM. The total diagnostic accuracy rate for GIM by LCI was 79.44%, higher than that of WLE (40.19%) ($P < 0.001$). Moreover, LCI with targeted biopsies showed a significantly increased ability to detect GIM ($P < 0.001$). PLC observed in the gastric mucosa on LCI can guide endoscopic biopsies and increase the detection rate of GIM. Thus, LCI could be a good tool for detecting GIM. ClinicalTrials.gov Identifier: ChiCTR-DDD-17011326)

Keywords Linked color imaging · Gastric intestinal metaplasia · White light endoscopy · Detection · Diagnosis

Introduction

Gastric intestinal metaplasia (GIM) is a precancerous lesion in the stomach [1, 2]. Since Correa et al. first described the cascade by which GIM progresses to gastric cancer (GC), GIM has become well-accepted as a premalignant lesion [3]. Patients with GIM have a sixfold increased risk of developing GC [4]. Shichijo et al. discovered that patients with severe atrophic gastritis and GIM remain at high risk of developing GC despite *Helicobacter pylori* eradication [5]. Hence, the close observation of patients with GIM may expedite the detection of late precancerous lesions and GC [6]. However, diagnosing GIM is currently entirely based on the histology of biopsy specimens, and the ability to detect GIM using white light endoscopy (WLE) is limited because GIM usually arises from the flat mucosa and features few morphological changes [7]. Buxbaum et al. demonstrated a low detection rate of GIM in patients at increased risk of developing GC [8]. Thus, a new method with a higher detection rate is needed.

Many studies have been performed using image-enhanced endoscopy (IEE), including confocal laser endomicroscopy, flexible spectral imaging color enhancement, narrow-band imaging (NBI), or autofluorescence imaging with a diagnostic yield of GIM of 65.70–86% [9–11]. Magnifying endoscopy with NBI is helpful in the diagnosis of GIM with a diagnostic yield exceeding 90% [12]. Many classifications of gastric mucosal patterns using magnifying NBI endoscopy were correlated with the histological observations of atrophy and GIM [13, 14]. However, these classifications are complex and difficult to understand (four types) [15]. Therefore, more simplified

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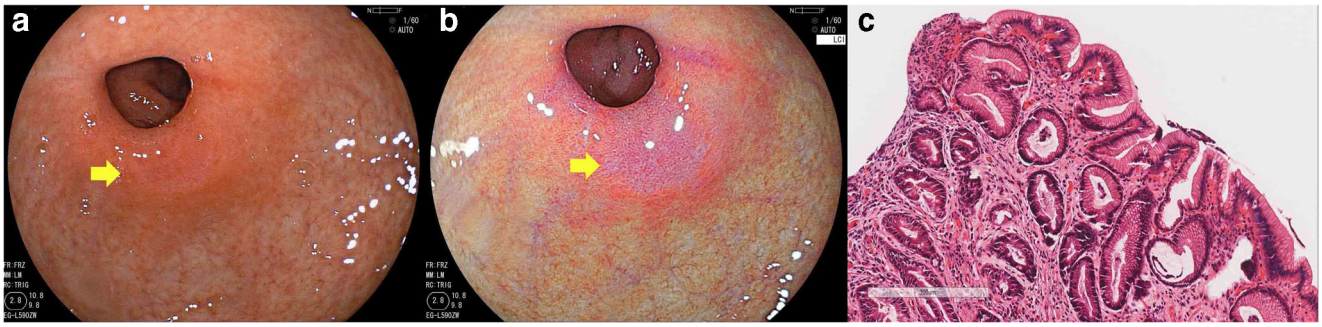

Fig. 1 Appearance of intestinal metaplasia in the antrum of the same participant under WLE and LCI models. **a** Endoscopic image in WLE shows a slight reddish lesion (yellow arrow). **b** After being switched to the LCI model, the lesions exhibit as a lavender color areas (yellow arrow). **c** Targeted biopsy shows intestinal metaplasia of the stomach (yellow arrow)

approaches with a high detection rate for GIM are needed in clinical practice.

A new IEE endoscope device, the LASERO system, was recently developed by FUJIFILM Corporation (Tokyo, Japan) [16]. This new device contains two laser sources. One is wide-spectrum white light illumination with a wavelength of 450 ± 10 nm, which is suitable for general observation, while the other has a narrow-band mode with a wavelength of 410 ± 10 nm [17]. The development of linked color imaging (LCI) was based on this new endoscope system with additional image processing to create bright and enhanced images [18]. In the LCI model, the red color was adjusted to make the lesions easy to detect [19]. A previous study indicated that the LCI technique could enhance the slight color differences in the endoscopic images, which may make the white region whiter and the red regions redder [19, 20]. LCI offers more data about the color alterations on the mucosal surface than that obtained with WLE [20]. Therefore, LCI may be able to detect flat lesions of the gastric mucosa that are greatly challenging to recognize using WLE. We recently found that a unique color feature detected on LCI, patchy lavender color (PLC), pathologically indicated GIM. This finding was similar to those of previous studies. Ono et al. indicated that, using the LCI model, GIM lesions appeared as a lavender color that is distinguishable from the circumferential mucosa without GIM [21]. Sun et al. reported that GIM appeared as a purple color on LCI [22]. However, these studies included limited cases and the detection accuracy rate of GIM by LCI endoscopy was not reported. Thus, the present study aimed to investigate whether LCI endoscopy could improve the detection accuracy of GIM by evaluating the hue characteristics on LCI images.

Participants and methods

Study design

This prospective trial was conducted at the Sixth Affiliated Hospital, Sun Yat-sen University, from February to May 2017. All participants provided written informed consent before the endoscopic investigation. This study was approved by the Ethics Committee of Sixth Affiliated Hospital, Sun Yat-sen University in accordance with the Declaration of Helsinki. All methods were performed following the relevant regulations and guidelines. This trial was registered with the Chinese Clinical Trial Registry (no. ChiCTR-DDD-17011326).

Participants

This study included 107 consecutive participants aged 40–75 years underdoing requiring endoscopic examinations between February and May 2017. We excluded participants with obvious late GC, a history of gastrectomy or partial gastric resection, the presence of digestive tract hemorrhagic diseases, or current anticoagulant intake. The participants' demographic and clinicopathological characteristics were retrieved from the endoscopy database.

Table 1 Demographic characteristics of participants included in the investigational study

Characteristic	*n* = 107
Age, mean (SD)	53.5 (10.6)
Gender	
Male	64
Female	43
Smoking	
Non-smoker	73
Current smoker	21
Former smoker	13
Alcohol	
Non-drinker	78
Current drinker	29
Helicobacter pylori infection	
Positive	45
Negative	62

Table 2 Diagnostic accuracy of endoscopy in participants with GIM by WLE and LCI

GIM	Sensitivity	Specificity	PPV	NPV	Accuracy
WLE	36.59% (15/41)*	42.42% (28/66)*	28.3% (15/53)*	51.85% (28/54)*	40.19% (43/107)*
LCI	90.24% (37/41)	72.72% (48/66)	67.27% (37/55)	92.31% (48/52)	79.44% (85/107)

PPV positive predictive value, *NPV* negative predictive value

*LCI versus WLE: $p < 0.001$

Endoscopic procedures and biopsies

All gastroscopies and biopsies were performed by experienced endoscopists with experience of performing more than 2000 cases of gastroscopy. All endoscopists were blinded to the participants' medical histories and conditions. Both WLE and LCI endoscopy were performed in all participants during the same procedure. The participants ingested simethicone solution (Zigong Honghe Pharmaceutical Co., Ltd. Sichuan, China) before the procedure. If poor visualization persisted, endoscopic flushing with simethicone solution was used to improve the visualization. Conscious sedation was administered to all participants. The stomach was first carefully examined using WLE by an experienced endoscopist. Since no guidelines have been established for GIM detection in WLE, we considered any abnormal mucosal change, including rough areas and localized discoloration, as indicative of GIM lesions in this study [8]. Another endoscopist who was blinded to the previous results then used LCI endoscopy to observe the stomach after WLE. As in a previous study [22], we defined LCI suspicious lesions for GIM as those with PLC that had both a lavender color and a regular mucosal pattern with a clear border (Fig. 1b). The location of the lesions discovered by WLE or LCI was recorded to obtain precise biopsies. If no abnormal lesions were found by WLE or LCI, five biopsies at the five standard locations of the stomach were obtained following the updated Sydney System classification [23].

Histopathologic evaluation

We used 4% formalin to anchor the specimens and embedded each in paraffin. The specimens were sliced into 4-μm sections and stained with hematoxylin and eosin. The histological analyses were performed by two expert gastrointestinal pathologists who were blinded to the endoscopic results. The histological diagnoses of chronic gastritis, GIM, and gastric neoplasia were documented following the updated Sydney System and modified Vienna criteria [23, 24]. GIM grade was evaluated using the updated Sydney System classification [23]. Each sample was evaluated for the presence of *H. pylori*.

Statistical analysis

In the per-participant analysis, the sensitivity values, specificity values, positive predictive values (PPV), negative predictive values (NPV), and diagnostic accuracy were calculated for predicting GIM. PPV and NPV definitions and the calculation method were described in previous reports [25, 26]. Participants with more than one lesion were considered as only one unit, and the most severe precancerous grade was recorded for the analysis. For example, if both chronic gastritis and GIM were detected in a participant, GIM was included in the final analysis. In the per-biopsy analysis, the accuracies of the targeted biopsies were calculated in each specimen in the LCI and WLE models. The chi-squared test was used to statistically compare the two groups. P values < 0.05 were considered statistically significant. Inter-observer agreements were analyzed using kappa values. Agreement strength was graded as follows: slight 0.01–0.2; fair 0.21–0.4; moderate 0.41–0.6; substantial 0.61–0.8; and almost perfect 0.81–1.0. All statistical analyses were performed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Participants' characteristics

A total of 107 participants (mean age 53.5 years; range 40–75 years) were included in this study. Participant demographics are listed in Table 1. Male participants represented 59.81% (64/107) of the cohort. In addition, 31.78% (34/107) of the participants were active smokers, while 27.1% (29/107) consumed alcohol. *H. pylori* was detected in 45 participants.

Per-participant analysis

The overall prevalence of GIM regardless of extent was 38.32% (41/107) in the histological analysis. GIM was detected in 13 (12.14%) participants by both LCI and WLE, whereas GIM was detected in 24 (22.43%) only by LCI and in 2 (1.87%) by WLE. GIM was found in 2 (1.87%) participants by random biopsy. Table 2 shows the sensitivity values, specificity values, PPV, NPV, and diagnostic accuracy of the LCI and WLE. The LCI had a significantly higher diagnostic

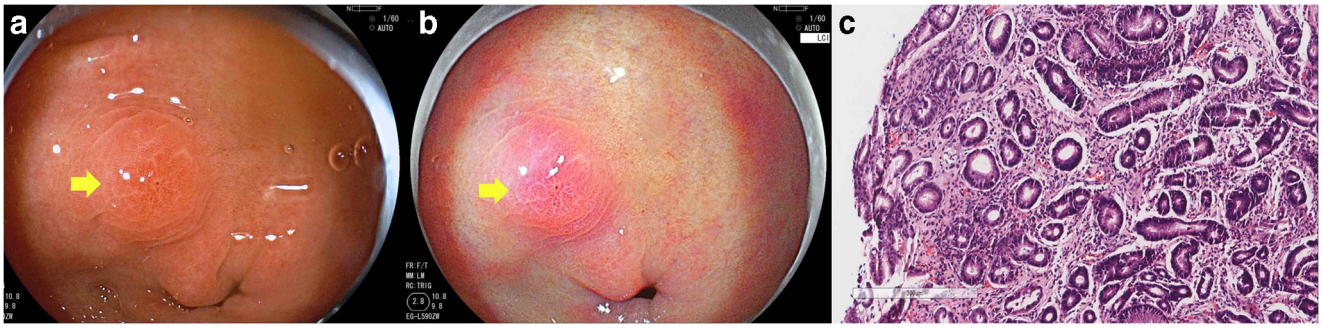

Fig. 2 Appearance of moderate inflammation in the antrum of the same participant under WLE and LCI models. **a** Endoscopic image in WLE shows a reddish lesion (yellow arrow). **b** After being switched to the LCI model, the lesions exhibit as a diffuse light lavender color areas (yellow arrow). **c** Targeted biopsy shows moderate inflammation of the stomach

accuracy rate than WLE (79.44% vs 40.19%; $P < 0.001$). The WLE findings had a sensitivity value of 36.59%, NPV of 51.85%, specificity of 42.42%, and PPV of 28.3% for WLE. The LCI findings had a sensitivity of 90.24%, NPV of 92.31%, specificity of 72.72%, and PPV of 67.27%.

Per-lesion analysis

For WLE, a total of 169 suspected lesion specimens were taken. Of them, 48 were histologically diagnosed as GIM, while 121 were diagnosed as chronic inflammation. For LCI, 198 suspected lesions were taken. Of them, 122 were diagnosed as GIM, 73 as chronic inflammation, and 3 as low-grade intraepithelial neoplasia. Hence, for the per-biopsy analysis, LCI significantly increased the diagnostic ability of GIM by targeted biopsies compared with WLE (61.6% [122/198)] versus 28.4% [48/169], respectively [$P < 0.001$]).

Inter-observer agreement

In the inter-observer agreement analysis, the mean kappa value on the detection of GIM was 0.63 (95% CI, 0.56–0.72) for WLE and 0.753 (95% CI, 0.615–0.846) for LCI. These results indicated substantial inter-observer agreement in WLE and LCI.

Discussion

LCI is a newly invented endoscopic system. LCI endoscopy images are brighter, making the red mucosal lesions easy to identify [27]. LCI endoscopy reveals large differences in color contrast between the suspicious lesion and the surrounding area, leading us to observe the suspicious lesion more carefully [28]. To date, no prospective data are available on the diagnostic utility and accuracy of LCI for detecting GIM in a population of an endoscopy unit in routine clinical practice.

Here, we investigated a specific color feature, PLC, in the gastric mucosa as seen in participants during routine LCI endoscopy. In areas with GIM, PLC was seen on LCI endoscopy. This investigation demonstrated that LCI can spot GIM in participants with a sensitivity of 90.24%, specificity of 72.72%, PPV of 67.27%, NPV of 92.31%, and diagnostic accuracy of 79.44%. All of these values in the LCI model were significantly higher than those of WLE. LCI gastroscopy significantly increased the per-biopsy detection rate of GIM by 32.5%, corresponding to a higher sensitivity of LCI than WLE (90.24% vs 36.59%%, $P < 0.001$). PLC seen on LCI endoscopy is closely correlated with GIM. The potential benefit of LCI detecting GIM using PLC might have important clinical implications.

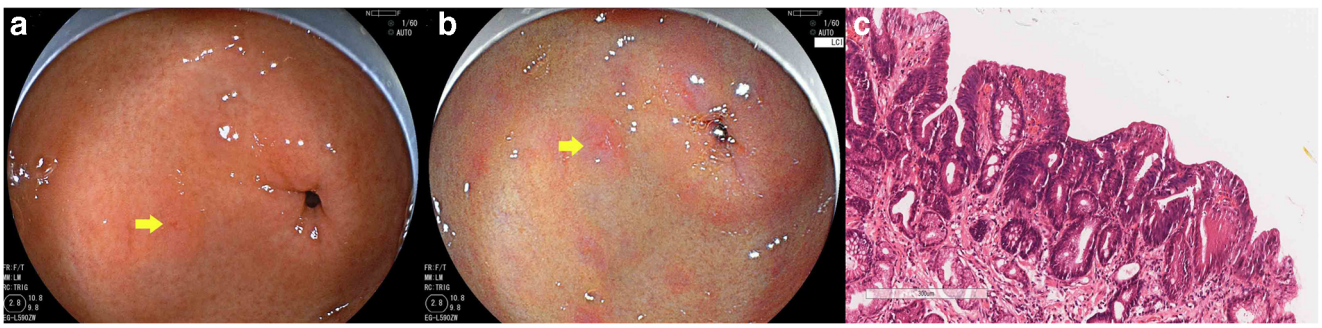

Fig. 3 Appearance of intestinal metaplasia in the antrum of the same participant under WLE and LCI models. **a** Endoscopic image in WLE shows a white opaque substance areas (yellow arrow). **b** After being switched to the LCI model, the lesions exhibit as a white opaque substance areas (yellow arrow). **c** Targeted biopsy shows intestinal metaplasia of the stomach (yellow arrow)

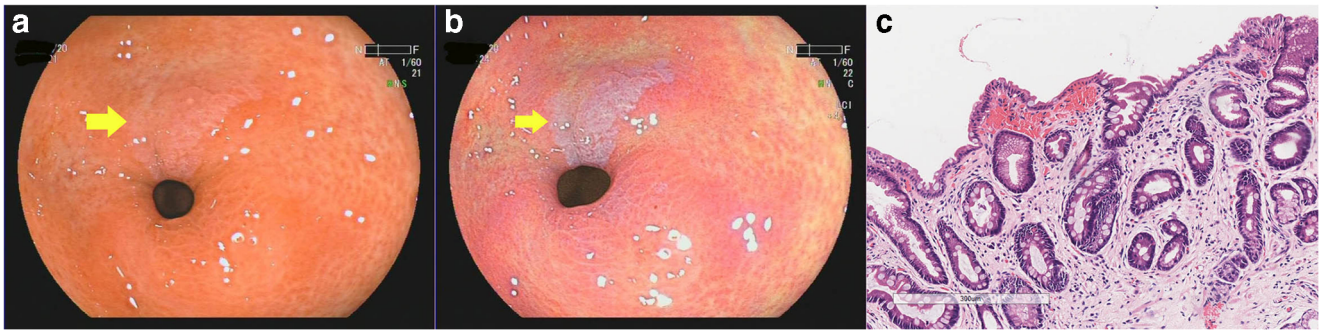

Fig. 4 Appearance of low-grade intraepithelial neoplasia in the antrum of the same participant under WLE and LCI models. **a** Endoscopic image in WLE shows a reddish lesion (yellow arrow). **b** After being switched to the LCI model, the lesions exhibit as a slightly reddish depressed lesion in a light lavender color area was observed (yellow arrow). **c** Targeted biopsy shows low-grade intraepithelial neoplasia and intestinal metaplasia of the stomach (yellow arrow)

However, the histological diagnosis of GIM was not confirmed in some PLC areas. Inflammation may present as a diffuse light lavender color without a clear border. Fifteen cases suspected as GIM by LCI were histologically diagnosed as moderate or severe inflammation. A retrospective review revealed lesions with a diffuse light lavender color without a clear border, some of which had erosions in the center (Fig. 2). A white opaque substance was found in the two cases solely diagnosed by WLE (Fig. 3). This finding was similar to those of Kanemitsu et al. and may lead to future research on this new identification marker of GIM [29]. Mild GIM and low-grade intraepithelial neoplasia were diagnosed in two lesions. A slightly reddish depressed lesion was observed in the PLC area (Fig. 4). This finding was similar to the pictures demonstrated by Ono et al. [21] and indicated that LCI may enhance the precancerous lesion in GIM. Moreover, no relationship was observed between the lavender color and GIM grade, meaning that this color may only predict the GIM in terms of pathologic diagnosis without a distinct grade. Two cases were detected by randomized biopsy; a diffuse red color was observed. Careful review of the pictures of these two cases revealed a slight lavender color in the deep diffuse red color area that was very difficult to identify (Fig. 5). These findings may explain the low specificity and should lead to a search for additional signs indicative of the presence of GIM on LCI endoscopy.

In our study, the inter-observer agreement was substantial, indicating that the classification of gastric antral lesions was substantial, possibly due to the complication of the concomitant occurrence with inflammation [30]. Although the changes in gastric mucosa microarchitecture were complicated in inflammatory and GIM lesions, LCI can enhance the GIM lesions through the detection of a lavender color and endoscopists can easily detect the GIM lesions.

This study had some limitations. First, this investigation was performed at a single center. A larger volume multicenter prospective studies should be performed to authenticate our observations. Second, because WLE and LCI were performed during the same procedure, a possible bias may exist in LCI endoscopy due to previous WLE observations. Third, although LCI showed an increased detection rate for GIM, it was also related to a high false positivity rate. Fourth, previous studies indicated that the incidence rate of GIM is age-related [31]. Thus, we only included participants older than 40 years old. The detection rate in participants younger than 40 years of age needs future investigation. Fifth, we cannot explain why GIM was observed as a lavender color in LCI. A previous report demonstrated that a light blue crest (LBC) under narrow-band light was a sign of the presence of GIM and was caused by differences in the reflectance of light at the surface of the brush border induced by GIM [32]. Ono et al.

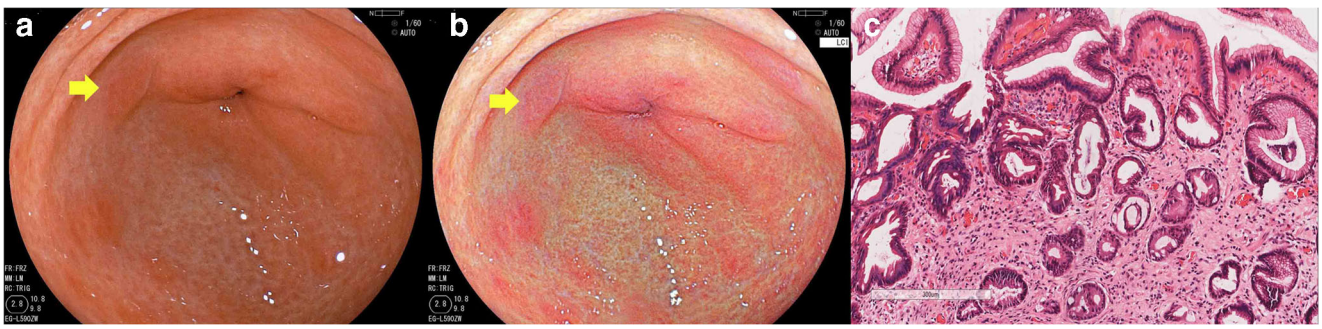

Fig. 5 Appearance of intestinal metaplasia in the antrum of the same participant under WLE and LCI models. **a** Endoscopic image in WLE shows a reddish lesion normal (yellow arrow). **b** After being switched to the LCI model, the lesions exhibit as a diffuse red color areas (yellow arrow). **c** Randomized biopsy shows intestinal metaplasia of the stomach (yellow arrow)

speculated that a lavender color on an LCI image is the same as the LBC or marginal turbid band [33]. Finally, a previous study reported that LBC is closely correlated with the histological assessment of GIM percentage [34]. However, in this study, lavender color intensities were not correlated with GIM levels. Further studies are needed to resolve the above issues.

In conclusion, the presence of a PLC in the gastric mucosa by LCI is a remarkably accurate pointer for GIM. This method can guide endoscopic biopsies and increase the detection rate of GIM. Thus, PLC observed by LCI is a useful endoscopic finding to detect histologic GIM, while LCI could be a good tool for detecting GIM.

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Compliance with ethical standards

The study was approved by the Ethics Committee of the Sixth Affiliated Hospital, Sun Yat-sen University and have been performed in accordance with the Declaration of Helsinki. The study was registered with Chinese Clinical Trial Registry (ChiCTR-DDD-17011381).

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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