J Gastric Cancer. 2021 Jun;21(2):142-154
https://doi.org/10.5230/jgc.2021.21.e13
pISSN 2093-582X·eISSN 2093-5641

Journal of Gastric Cancer

Original Article

Appropriate Color Enhancement Settings for Blue Laser Imaging Facilitates the Diagnosis of Early Gastric Cancer with High Color Contrast

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Received: Dec 24, 2020
Revised: Apr 11, 2021
Accepted: May 30, 2021

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ABSTRACT

Purpose: Screening image-enhanced endoscopy for gastrointestinal malignant lesions has progressed. However, the influence of the color enhancement settings for the laser endoscopic system on the visibility of lesions with higher color contrast than their surrounding mucosa has not been established.

Materials and Methods: Forty early gastric cancers were retrospectively evaluated using color enhancement settings C1 and C2 for laser endoscopic systems with blue laser imaging (BLI), BLI-bright, and linked color imaging (LCI). The visibilities of the malignant lesions in the stomach with the C1 and C2 color enhancements were scored by expert and non-expert endoscopists and compared, and the color differences between the malignant lesions and the surrounding mucosa were assessed.

Results: Early gastric cancers mainly appeared orange-red on LCI and brown on BLI-bright or BLI. The surrounding mucosae were purple on LCI regardless of the color enhancement but brown or pale green with C1 enhancement and dark green with C2 enhancement on BLI-bright or BLI. The mean visibility scores for BLI-bright, BLI, and LCI with C2 enhancement were significantly higher than those with C1 enhancement. The superiority of the C2 enhancement was not demonstrated in the assessments by non-experts, but it was significant for experts using all modes. The C2 color enhancement produced a significantly greater color difference between the malignant lesions and the surrounding mucosa, especially with the use of BLI-bright (P=0.033) and BLI (P<0.001). C2 enhancement tended to be superior regardless of the morphological type, *Helicobacter pylori* status, or the extension of intestinal metaplasia around the cancer.

Conclusions: Appropriate color enhancement settings improve the visibility of malignant lesions in the stomach and color contrast between the malignant lesions and the surrounding mucosa.

Keywords: Image enhancement; Lasers; Gastric cancer; Diagnosis; Endoscopy

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Screening image-enhanced endoscopy for gastrointestinal malignancies has progressed, and it facilitates a high color contrast between malignant lesions and their surrounding mucosae [1-4]. Linked color imaging (LCI) produces bright and vivid images for distant views and is useful in the stomach with its wide lumen [5-7]. Blue laser imaging (BLI) has a higher emission intensity at 410 nm, a shorter wavelength, and facilitates better visualization of microstructural and microvascular images than LCI and white light imaging (WLI) [6]. In addition, BLI facilitates a high color contrast between lesions and their surrounding mucosae at a near view, which leads to advantages in detecting malignant gastric lesions and identifying the demarcation line [8]. However, BLI shows different colors in the gastric mucosa among several previously reported images [2,3,9-11]. This color information may influence the precision of diagnosis of malignant lesions. Different colors may originate from the color enhancement (color tone) chosen by endoscopists for the endoscopic system. Most endoscopists may not consider that mucosal colors in the gastrointestinal tract vary largely with color enhancement settings because most authors reported BLI with initial settings (C1 color enhancement).

Some endoscopists have already reported that the adaptive index of hemoglobin color enhancement increases the detection rate of superficial colonic tumors when using a xenon endoscopic system [12-14]. Color enhancement for a laser endoscopic system results in red, white, and green colors becoming redder, whiter, and greener, respectively. The latest laser endoscopic system developed in 2017 is equipped with an over-megapixel complementary metal-oxide semiconductor (CMOS) image sensor, a new light source, and a video processor, and can provide high-quality images of the gastrointestinal tract. However, the specific details of the color enhancement settings useful for the accurate diagnosis of early gastric cancer are unknown. This uncertainty led to this study involving a new laser endoscopic system designed to assess the visibility of the delineation of malignant gastric lesions and the color differences between malignant lesions and surrounding mucosa.

MATERIALS AND METHODS

Before the endoscopic submucosal dissection (ESD) of early gastric cancers, the prospectively collected data of 220 consecutive patients who underwent detailed examination with the latest laser endoscopic system (EG-L600ZW, LL-7000 light source, and VP-7000HD; Fujifilm Co., Tokyo, Japan) between October 2018 and December 2019 were reviewed. The patients underwent esophagogastroduodenoscopy with a laser endoscope (EG-L600ZW), which involved WLI, LCI, BLI-bright, and BLI as time permitted. However, these detailed examinations took time to complete in several patients because they included endoscopic ultrasonography for evaluating the depth of tumor invasion. We aimed to evaluate the color contrast between early gastric cancer and the surrounding mucosa on LCI, BLI-bright, and BLI with C1 and C2 color enhancement settings. With a simple push of a button for the color enhancement function on the processor, an endoscopist can switch from one setting to another, resulting in dramatic mucosal color changes, especially when using BLI. Satisfactory LCI, BLI-bright, and BLI with color enhancement settings as well as WLI were performed for 67 early gastric cancer lesions in 61 patients. All the lesions were diagnosed as early gastric cancer limited to the mucosa or submucosa.

https://doi.org/10.5230/jgc.2021.21.e13

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This study was approved by the Institutional Review Board and the ethics committee of Jichi Medical University (approval number: A19-145) and adhered to the ethical principles of the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained using an opt-out form on the website of Jichi Medical University, and no patient was rejected.

Six endoscopists (YH, YM, HO, YN, HT, MT), each with at least 3 years of experience with endoscopic procedures using the laser endoscopic system, performed the endoscopic evaluations. Gastric cancer is often covered with mucus. The mucus on the surfaces of the malignant lesions was removed by washing with water. The surfaces and vascular patterns were evaluated in detail using near and magnified images, although the endoscopists knew that bleeding could result. Of 67 lesions, mucosal bleeding occurred in 25 lesions during the examination, and 1 patient died before ESD. One lesion contained undifferentiated carcinoma according to a review of the biopsy and ESD specimens. The invasions of the surrounding mucosa by the aforementioned lesion differ from those by a differentiated adenocarcinoma. Therefore, these 27 lesions were excluded, and 40 lesions in 34 patients (6 double cancers) were included in the final analysis. **Fig. 1** shows a flowchart for the process from the endoscopic observation to the analysis of these lesions.

The mean tumor size was 16.3±12.1 mm. Of these lesions, 17 were elevated, 8 were flat, and 15 were depressed. The pathological findings of the lesions resected by ESD included 35 well-differentiated and 5 moderately differentiated adenocarcinomas. The characteristics of the lesions are listed in **Table 1**. The locations of the malignant lesions were categorized into

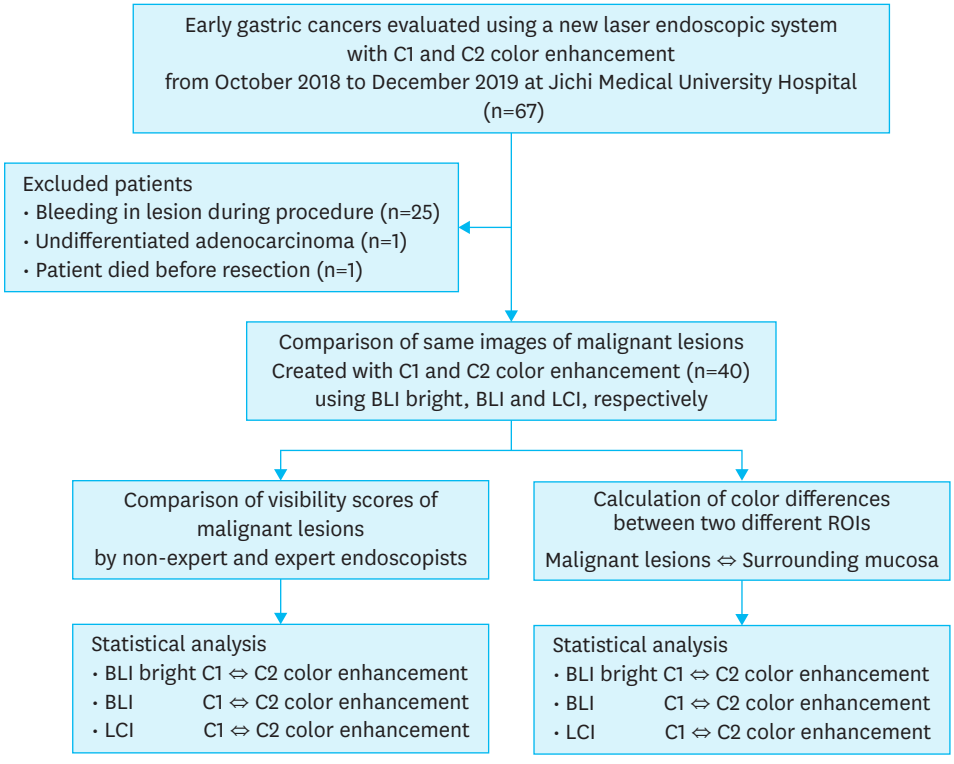

Fig. 1. Study protocol including the visibility of early gastric cancers evaluated by endoscopists and comparison of color differences between malignant lesions and their surrounding mucosa on WLI, BLI-bright, BLI, and LCI and based on the histological findings of the resected specimens.
WLI = white light imaging; BLI = blue laser imaging; LCI = linked color imaging.

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Table 1. Clinical characteristics, endoscopic findings, and pathological findings

Parameter	Value (n=40 lesions in 34 patients)
Age (yr)*	72.7±9.2
Sex, male*	28 (82.4)
Tumor size (mm)	
Endoscopic tumor size	16.3±12.1
Histological tumor size of resected specimens	16.7±11.2
Location	
Proximal/Middle/Distal portion	5/12/23
Color of white light imaging	
Redder/Similar color as surroundings/Discolored	5/32/3
Morphology, n (%)	
Elevated	17 (42.5)
Flat	8 (20.0)
Depressed	15 (37.5)
Helicobacter pylori status, n (%)*	
Positive	10 (29.4)
Negative	5 (14.7)
Eradicated	18 (52.9)
Undetermined	1 (2.9)
Procedure for resection, n (%)	
Endoscopic submucosal dissection	40 (100.0)
Depth of cancer in resected specimens, n (%)	
m	37 (92.5)
sm 1	2 (5.0)
sm 2	1 (2.5)
Pathological findings of resected specimens, n (%)	
tub1/tub2	35/5

Values are presented as mean±standard deviation or number (%).
m = intramucosal cancer; sm 1 = cancer with shallow submucosal invasion; sm 2 = cancer invaded deep submucosa; tub1 = well-differentiated adenocarcinoma; tub2 = moderately differentiated adenocarcinoma.
*Each value is described based on the number of patients.

the proximal, middle, and distal parts of the stomach. The malignant lesions were classified based on the Paris classification [15]. The maximum diameter of a malignant lesion or tumor in the resected specimens was used as the size.

The visibility of the delineation of malignant lesions was evaluated using C1 and C2 color enhancements. Six sets of the same still images of malignant lesions with appropriate brightness were selected from the endoscopic images obtained with BLI-bright, BLI, and LCI including C1 and C2 color enhancements, respectively (40 images for each mode and 240 images in total). The visibilities of the delineations of the malignant lesions were evaluated using published visibility scores [16] ranging from 1 to 4. A score of 4 indicated excellent visibility; it was easy to recognize the delineation. A score of 3 indicated good visibility; if an endoscopist looked in the same direction as the lesion in the image, it was easy to detect the delineation. A score of 2 indicated fair visibility; it was difficult to detect a demarcation line without careful observation. A score of 1 indicated poor visibility. Representative images of visibility with scores of 1–4 are shown in **Fig. 2**. The images were evaluated by 6 other endoscopists who had not seen any of the images before this study and were not among the 6 endoscopists who performed the examinations and acquired the images. Of the 6 endoscopists, three were classified as non-experts (had not used or learned detailed examination by themselves for upper gastrointestinal lesions using BLI-bright, BLI, and LCI) and three were classified as experts (had used and learned detailed examinations for two years or more). The experts had at least two years of experience with similar numbers of detailed endoscopic examinations using LCI, BLI-bright, and BLI in the educational program

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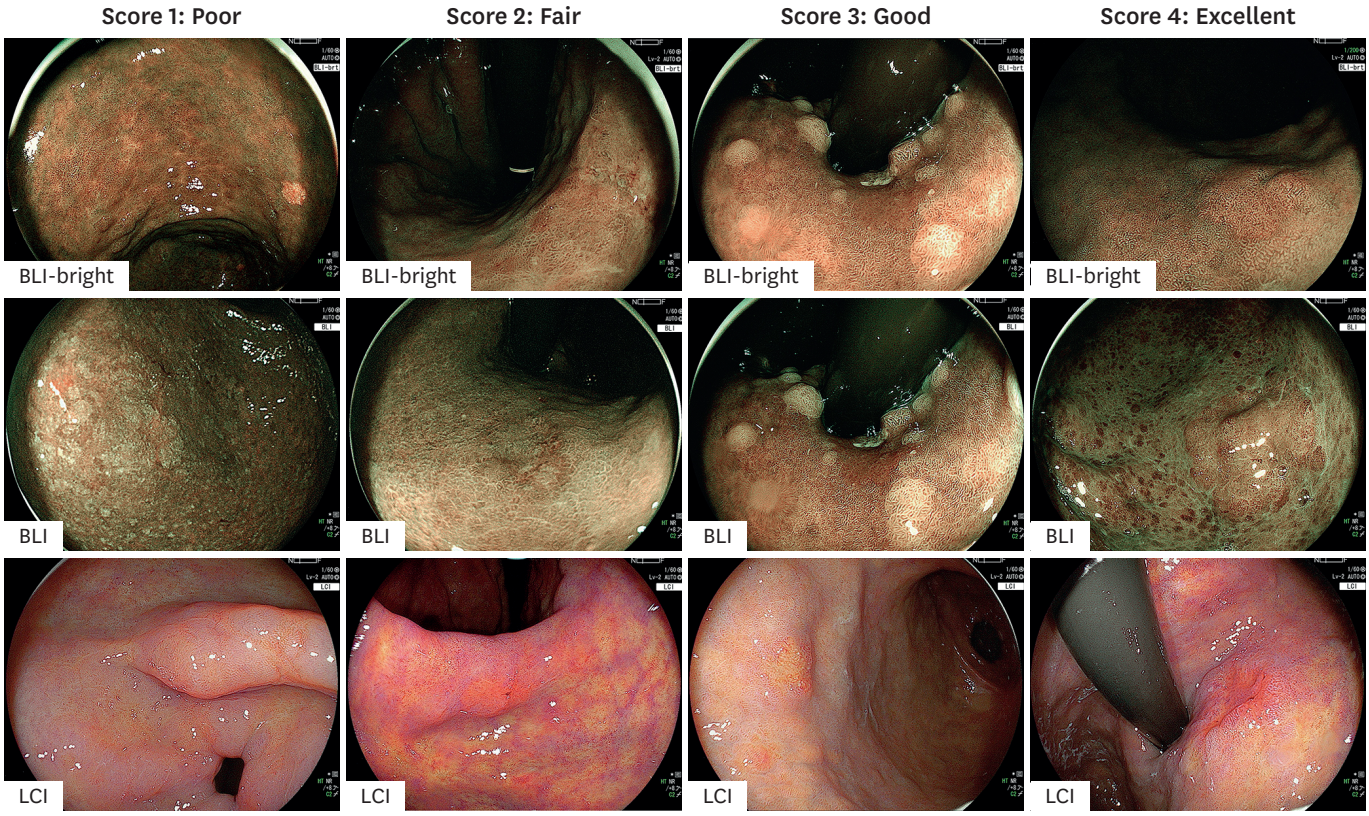

Fig. 2. Representative images with visibility scores ranging from 1 to 4.
BLI = blue laser imaging; LCI = linked color imaging.

at our institution. We believe that a program of this duration is necessary to acquire sufficient knowledge and skills. All images (n=240) were randomly evaluated.

In addition, colorimetric evaluations involving WLI, BLI-bright, BLI, and LCI were performed. The images were analyzed objectively based on the L*a*b* (L*=light/dark; a*=red green; b*=yellow blue) color values in the CIELAB system using Adobe Photoshop CC2019, as previously reported [5,6,17]. The region of interest (ROI; 20×20 pixels) was selected for the malignant lesions and the surrounding mucosa. The average of the five median RGB values for the five sample points was calculated for each region. The L*a*b* values were calculated from the average RGB values. The color difference ($\Delta E^* = [(\Delta L^*)^2+(\Delta a^*)^2+ (\Delta b^*)^2]^{1/2}$) of the pixel values was used to evaluate the color contrast between the malignant lesions and the surrounding mucosa on the images acquired with LCI, BLI-bright, and BLI with C1 and C2 color enhancements and WLI.

The color differences were classified by morphology, *Helicobacter pylori* status, and the histological presence of intestinal metaplasia adjacent to the cancer in the resected specimens as follows. The histological findings of the mucosa in the entire circumference just adjacent to the cancer were assessed for the manifestations of intestinal metaplasia in such areas. The proportion of intestinal metaplasia around the circumference of the cancer was calculated based on the presence of metaplastic changes at the lateral margins of all the pathological sections, including the malignant portion, as previously described [6]. For example, five sections, including the malignant portions, had 10 lateral sides. If eight of these lateral sides had adjacent intestinal metaplasia, the proportion was 80%. The

https://doi.org/10.5230/jgc.2021.21.e13

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proportions were compared with the color differences between the malignant lesions and the surrounding mucosa.

Statistical analysis

The statistical analyses were carried out using SPSS (version 26.0, Macintosh; IBM, Armonk, NY, USA). The visibility scores for the C1 and C2 color enhancements are expressed as mean (standard deviation), and they were compared using the 2-tailed paired t-test. The distributions of the visibility scores by the non-experts and experts were compared using the linear-by-linear χ^2 test. The inter-observer agreement for the visibility scores was assessed using Fleiss' kappa values. The color differences and the values of L*, a*, and b* associated with the C1 and C2 color enhancements were expressed as median (1st quartile–3rd quartile) and compared using the Wilcoxon signed rank test. Similarly, the color difference levels for WLI and BLI-bright, BLI, and LCI were compared. Statistical significance was set at $P<0.05$.

RESULTS

Early gastric cancers appeared orange-red on LCI and brown on BLI-bright or BLI. The surrounding mucosae were purple on LCI, which corresponds to the green mucosa on BLI and the histological intestinal metaplasia. However, the colors of the surrounding mucosae were different for the 2 color enhancement settings using BLI or BLI-bright. The C1 color enhancement resulted in brown or pale green surrounding mucosa, while the C2 color enhancement resulted in dark-green surrounding mucosa (**Fig. 3**).

We compared the visibilities after using the C1 and C2 color enhancements for BLI-bright, BLI, and LCI. The visibility scores were determined by six endoscopists, including three experts and three non-experts, as reported previously [18,19]. The mean visibility scores using the C2 enhancement for BLI-bright, BLI, and LCI were significantly higher than those using the C1 enhancement (**Table 2**). However, the superiority of the C2 enhancement was not observed when evaluations were performed by non-experts (BLI-bright, P=0.26; BLI, P=0.63; LCI, P=0.36), but it was significantly improved for experts for all modes (BLI-bright and BLI, P<0.001; LCI, P=0.01) (**Table 2**, **Fig. 4**). It is important to evaluate whether poor visibility improves with a different color-enhancement setting. The distributions of the visibility scores were compared for the C1 and C2 color enhancements in each mode (**Fig. 4**). For the non-expert

Table 2. Mean visibility scores of early gastric cancers on BLI-bright, BLI, and LCI

Color enhancement	C1	C2	P-values
BLI-bright			
All	2.78±1.00	3.01±0.94	<0.001
Non-expert	2.83±1.03	2.90±0.97	0.26
Expert	2.74±0.97	3.13±0.89	<0.001
BLI			
All	2.86±0.93	3.03±0.96	0.002
Non-expert	2.95±0.93	2.92±0.96	0.63
Expert	2.77±0.91	3.13±0.96	<0.001
LCI			
All	3.05±0.89	3.18±0.87	0.01
Non-expert	2.88±0.88	2.93±0.91	0.36
Expert	3.23±0.88	3.42±0.75	0.01

Values are presented as mean±standard deviation.
BLI = blue laser imaging; LCI = linked color imaging.

https://doi.org/10.5230/jgc.2021.21.e13

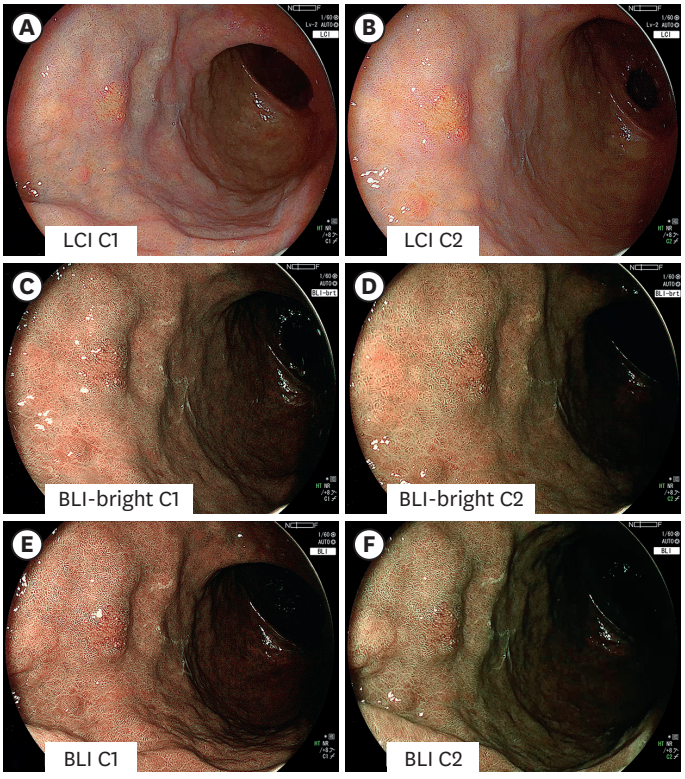

Fig. 3. Representative images of early gastric cancer. LCI with (A) C1 and (B) C2 color enhancement. Orange-red cancer is surrounded by purple mucosa. (C) BLI-bright with C1 color enhancement. (D) BLI-bright with C2 color enhancement. (E) BLI with C1 color enhancement. (F) BLI with C2 color enhancement. On BLI-bright and BLI, brown cancers are surrounded by pale green mucosa with C1 color enhancement and dark green mucosa with C2 color enhancement. Dark green mucosae have a greater color contrast relative to the cancer.
LCI = linked color imaging; BLI = blue laser imaging.

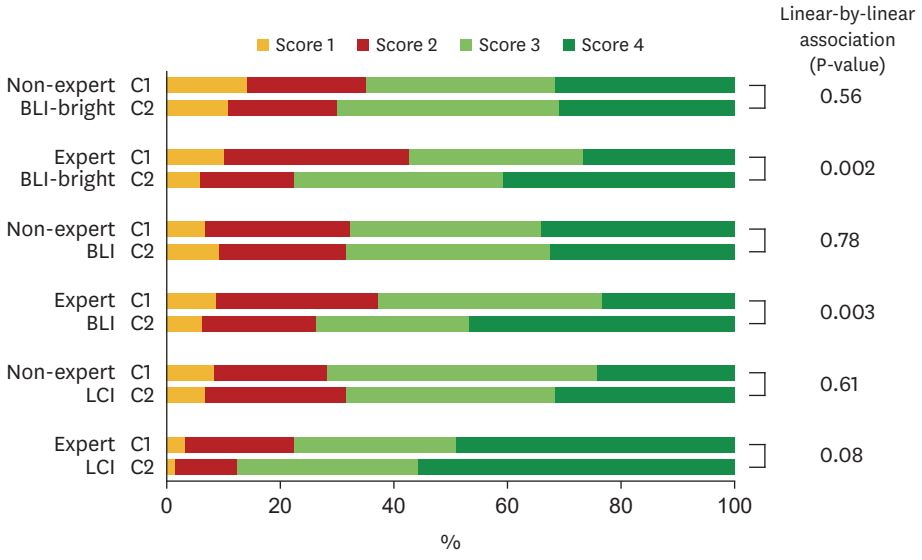

Fig. 4. Graphic distribution of visibility scores by expert endoscopists using BLI-bright, BLI, and LCI showing the superiority of C2 color enhancement. Scores from 1 to 4 represent poor, fair, good, and excellent visibilities, respectively. The statistical values were derived by the linear-by-linear association χ^2 test.
BLI = blue laser imaging; LCI = linked color imaging.

https://doi.org/10.5230/jgc.2021.21.e13

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evaluators, the distributions of the scores for the C1 and C2 color enhancements in each mode were similar as evaluated by the linear-by-linear association χ^2 test. However, the scores tended to be higher with the C2 color enhancement than with the C1 enhancement for the experts, especially with the use of BLI-bright (P=0.002) and BLI (P=0.003).

Poor visibility was scored as 1 or 2, while good visibility was scored as 3 or 4. Concerning the analysis of inter-observer agreement for poor and good visibility, Fleiss's kappa values for the three non-expert and three expert endoscopists were calculated for each mode. The mean kappa value of 0.476 (95% confidence interval, 0.474–0.478) for the experts was higher than the 0.350 (0.348–0.353) for the non-experts when all the images were evaluated. The kappa values for the experts were 0.506 (0.502–0.510) for BLI-bright, 0.350 (0.346–0.354) for BLI, and 0.567 (0.563–0.571) for LCI. The kappa values for the non-experts were 0.297 (0.293–0.301) for BLI-bright, 0.369 (0.365–0.373) for BLI, and 0.385 (0.381–0.389) for LCI.

In addition, the color differences were evaluated by comparing the malignant lesions and the surrounding mucosa. The color differences with both C1 and C2 color enhancements for BLI-bright, BLI, and LCI were significantly higher than those for WLI (P<0.001) (**Table 3**). The color differences using C1 and C2 color enhancements for BLI-bright, BLI, and LCI were compared. There was no significant color difference for the LCI mode (P=0.132). For the BLI-bright mode, the color difference with the C2 enhancement was significantly higher than that with the C1 enhancement (P=0.033). For the BLI mode, the color difference with the C2 enhancement was significantly greater than that with the C1 enhancement (P<0.001). The C2 color enhancement seemed to be mainly associated with high values of ⊿a in the red-green component (**Table 3**). These results imply that the surrounding dark-green mucosa adjacent to the malignant lesion with the C2 color enhancement enables the recognition of the malignant lesion and the detection of its demarcation line.

Table 3. Comparison of the color differences between cancers and their surrounding mucosa on WLI, BLI-bright, BLI, and LCI (n=40)

Variables			P-value
⊿E			
White Light Images	7.0 (5.2 to 9.0)		
BLI-bright with C1		9.1 (6.3 to 13.1)	vs. WLI <0.001
BLI-bright with C2		10.7 (7.2 to 14.4)	vs. WLI <0.001
BLI with C1		10.1 (6.7 to 13.1)	vs. WLI <0.001
BLI with C2		11.6 (8.3 to 16.7)	vs. WLI <0.001
LCI with C1		13.8 (9.6 to 16.8)	vs. WLI <0.001
LCI with C2		12.2 (9.7 to 16.4)	vs. WLI <0.001
Color enhancement	C1	C2	
BLI-bright			
⊿E	10.0 (6.4 to 13.3)	10.7 (8.0 to 14.7)	0.033
⊿L	−3.4 (−9.0 to 1.8)	−4.7 (−9.5 to 3.5)	0.472
⊿a	4.4 (2.9 to 7.6)	5.4 (2.9 to 7.4)	0.291
⊿b	1.8 (−0.1 to 3.5)	1.2 (−0.3 to 3.6)	0.301
BLI			
⊿E	10.4 (7.1 to 13.1)	12.1 (8.2 to 16.8)	<0.001
⊿L	−3.5 (−8.0 to 1.2)	−5.0 (−11.8 to 3.5)	0.307
⊿a	5.3 (1.8 to 8.0)	6.2 (3.6 to 8.4)	0.139
⊿b	1.4 (0.4 to 3.4)	1.3 (−0.4 to 2.8)	0.075
LCI			
⊿E	13.8 (10.5 to 16.3)	11.9 (10.2 to 15.8)	0.132
⊿L	1.0 (−3.4 to 4.6)	0.9 (−2.8 to 4.7)	
⊿a	2.7 (−3.5 to 10.6)	2.4 (−3.3 to 7.6)	
⊿b	7.7 (4.9 to 12.6)	8.0 (5.3 to 12.4)	

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Table 3. (Continued) Comparison of the color differences between cancers and their surrounding mucosa on WLI, BLI-bright, BLI, and LCI (n=40)

Variables			P-value
Morphology			
White Light Images ⊿E			
Elevated (n=17)	7.2 (5.7 to 9.0)		
Flat (n=8)	4.8 (4.2 to 8.5)		
Depressed (n=15)	6.8 (4.9 to 9.7)		
Color enhancement	C1	C2	
BLI-bright ⊿E			
Elevated (n=17)	10.5 (7.7 to 13.2)	11.0 (7.1 to 15.1)	0.149
Flat (n=8)	6.5 (4.9 to 10.0)	8.2 (6.4 to 11.5)	0.012
Depressed (n=15)	8.9 (6.2 to 13.0)	9.9 (7.2 to 12.9)	0.91
BLI ⊿E			
Elevated (n=17)	8.6 (5.9 to 12.6)	12.1 (8.2 to 16.6)	0.002
Flat (n=8)	10.1 (6.3 to 12.0)	10.0 (7.7 to 14.3)	0.093
Depressed (n=15)	10.5 (8.1 to 13.9)	11.5 (8.3 to 16.6)	0.017
LCI ⊿E			
Elevated (n=17)	12.9 (9.6 to 17.0)	11.8 (9.6 to 15.8)	0.723
Flat (n=8)	11.5 (8.3 to 15.4)	10.3 (7.6 to 12.3)	0.124
Depressed (n=15)	14.1 (10.6 to 16.4)	13.4 (10.2 to 16.7)	0.91
Rate of pathological circumferential intestinal metaplasia	C1	C2	
>75% (n=30)			
BLI-bright ⊿E	8.9 (6.0 to 12.5)	9.9 (7.1 to 11.6)	0.079
BLI ⊿E	8.4 (6.4 to 12.3)	11.1 (8.2 to 15.0)	<0.001
≤75% (n=10)			
BLI-bright ⊿E	13.5 (10.0 to 14.4)	14.6 (11.8 to 17.0)	0.263
BLI ⊿E	12.2 (9.9 to 15.5)	14.8 (9.3 to 18.7)	0.028
>50% (n=35)			
BLI-bright ⊿E	9.0 (6.2 to 12.6)	10.5 (7.2 to 13.7)	0.019
BLI ⊿E	9.7 (7.0 to 12.3)	11.5 (8.3 to 15.4)	<0.001
≤50% (n=5)			
BLI-bright ⊿E	14.1 (13.9 to 15.9)	15.4 (4.2 to 18.1)	0.893
BLI ⊿E	13.5 (5.3 to 15.7)	18.6 (6.7 to 18.7)	0.043
Helicobacter pylori status	C1	C2	
Negative (n=5)			
BLI-bright ⊿E	12.5 (6.6 to 14.2)	8.3 (7.2 to 15.1)	0.502
BLI ⊿E	8.0 (7.2 to 13.1)	8.0 (8.0 to 16.7)	0.08
Positive (n=12)*			
BLI-bright ⊿E	10.5 (8.5 to 12.8)	10.9 (9.5 to 13.5)	0.53
BLI ⊿E	8.4 (7.8 to 10.9)	9.5 (8.3 to 12.9)	0.028

Data are shown as median (1st quartile–3rd quartile).
⊿E* shows the color difference and is calculated using the following formula: $[(\Delta L^*)^2+(\Delta a^*)^2+(\Delta b^*)^2]^{1/2}$. L^* is defined as lightness, a^* is the red-green component, and b^* is the yellow-blue component. ⊿L is obtained from the formula: (absolute L of malignant lesion − absolute L of surrounding mucosa) × 100/255. Values (⊿a, ⊿b) were obtained by subtracting the value for the surrounding mucosa from the value for the malignant lesion. WLI = white light imaging; BLI = blue laser imaging; LCI = linked color imaging. *Two double cancers were included.

We examined the factors that may influence the observed color differences between the BLI-bright and BLI with the C1 and C2 color enhancements. For the BLI modes, the color difference tended to be greater with the C2 color enhancement than with the C1 color enhancement for the elevated and depressed early gastric cancers; however, the differences were similar for the flat lesions (**Table 3**). For the BLI-bright mode, the color difference was greater with the C2 color enhancement than with the C1 color enhancement for the flat lesions but similar for the elevated and depressed types. The statistical findings varied with the morphological types (**Table 3**). The superiority of the C2 color enhancement was more pronounced with BLI than with BLI-bright in the *H. pylori*-infected mucosa (**Table 3**).

https://doi.org/10.5230/jgc.2021.21.e13

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Pathological intestinal metaplasia is closely associated with purple and green lesions when using LCI and BLI, respectively [5,20,21]. In this study, we evaluated the influence of these mucosal changes on the color difference between the malignant lesion and the surrounding mucosa with C1 and C2 color enhancements. We divided the images into 2 subgroups, where intestinal metaplasia accounted for more than 75% of all pathological sections and less than 75%, as reported previously [6].

We further evaluated the images and designated some of them to another subgroup characterized by intestinal metaplasia accounting for more than 50% and less than or equal to 50% of the pathological sections. Regardless of the values of the boundary, including 75% and 50%, BLI showed significantly greater color differences with the C2 than the C1 color enhancement (**Table 3**). BLI-bright showed significantly greater color differences with the C2 color enhancement than with the C1 color enhancement with a higher distribution (>50%) when divided at a boundary of 50%, but there were no significant differences when divided at a boundary of 75%. These data imply that BLI has a significantly greater color contrast using the C2 color enhancement in the mucosa surrounding the cancer in tissues with greater and lesser distributions of intestinal metaplasia.

DISCUSSION

In this study, color enhancement settings for the BLI-bright and BLI modes subjectively and objectively affected the color contrast between the malignant lesions and the surrounding mucosa in the stomach, as shown by the visibility scores and color differences. All malignant lesions were recognized as brown with both C1 and C2 color enhancements. However, the surrounding mucosae appeared brown or pale green when imaged with the C1 color enhancements and dark green when imaged with the C2 color enhancements. The C2 color enhancement was significantly associated with better visibility of a malignant lesion and greater color contrast delineating it from the surrounding mucosa. These findings imply that C2 color enhancement for the aforementioned modes is more useful for identifying a malignant lesion in the stomach and determining its delineation from its surrounding mucosa.

In contrast with the color enhancement associated with hemoglobin using xenon endoscopy [12-14], the color enhancement in a laser endoscopic system is associated with the balance of colors, including blue, green, and red, although the settings have not been described in detail. We demonstrated that the C2 color enhancement was associated with higher visibility scores for early gastric cancers determined by expert endoscopists than by non-experts. This suggests that experience using BLI-bright and BLI is necessary to achieve a high level of diagnostic accuracy for early gastric cancers. In this study, the non-experts had little or no experience with using LCI and BLI for the diagnosis of early gastric cancer. Therefore, they could recognize colorful images of early gastric cancers in colored background mucosa, but they could not judge whether they contained cancer or not.

Endoscopic treatments such as ESD have progressed and require a precise line of demarcation between the malignant lesion and the surrounding mucosa. BLI produces higher resolution images at closer distances than LCI [3], which allows better determination of the delineation of early gastric cancer. However, the BLI in previous reports seems to have been performed with C1 color enhancement because the surrounding mucosa was not dark-green. We have reported that BLI provides a dark-green color in the surrounding mucosa,

https://doi.org/10.5230/jgc.2021.21.e13

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resulting in a high color contrast with the malignant lesion [3,8]. In the current study, we demonstrated the objective superiority of the C2 color enhancement with BLI-bright and BLI over the C1 color enhancement for the diagnosis of early gastric cancers because of the greater color differences. In clinical practice, C2 color enhancement with BLI-bright may be useful for observing farther lesions, while BLI is useful for nearer lesions.

Most green and purple colors of the surrounding mucosa are consistent with tissue that is histologically shown to be intestinal metaplasia [3,6,20]. However, some biopsy specimens from the purple gastric mucosa are not consistent with intestinal metaplasia [6]. Purple and green may result from a scarcity of glandular cells and/or vessels in the superficial layer, such as regenerative mucosa and hyperplastic polyps [22,23]. Not all early gastric cancers are surrounded by intestinal metaplasia [6]. In addition, some cancers were partially surrounded, while others were not, in this study. We evaluated the incidence of pathologically demonstrated intestinal metaplasia in the surrounding mucosa using endoscopically resected specimens. The color differences are greater when using C2 rather than C1 color enhancement for lesions even when intestinal metaplasia is less distributed and other histological changes are present around the cancer instead. Dark-green mucosa with C2 color enhancement may be useful for visualizing malignant lesions and its color contrast delineating it from the surrounding mucosa even if intestinal metaplasia is not present in all areas of the surrounding mucosa.

Using LCI, the visibility scores with C2 color enhancement were higher than those with C1, but the color difference between the malignant lesions and the surrounding mucosa was similar for both enhancements. These similar color differences may be attributed to the similar colors of the surrounding mucosa, although there are shades of purple, which may have resulted in the different visibility scores. The BLI-bright and BLI modes are associated with high visibility scores and color differences when C2 color enhancement is used. Some images of the surrounding mucosa with the BLI-bright and BLI mode are brown or pale-green with C1 color enhancement and dark-green with C2 color enhancement. The different colors of the surrounding mucosa result in different visibilities and color differences. However, LCI includes red, blue, and green colors, and they are different from those of the BLI, which includes only blue and green. In addition, the balance of these colors for each type of color enhancement was independently set for the BLI-bright, BLI, and LCI modes. Therefore, it may not be appropriate to compare the color differences for the LCI and BLI modes when discussing the C1 and C2 color enhancements. However, the visibility scores were higher with the C2 color enhancement for all the modes, suggesting that this enhancement provides more information for the diagnosis of early gastric cancers.

This study has some acknowledged limitations. First, this was a single-center retrospective study. Second, undifferentiated carcinomas were not evaluated. Mucosal scars from previous biopsies may have also influenced the pathological findings of the resected specimens.

In summary, the color enhancement settings for the BLI-bright and BLI modes significantly influenced the color contrast of the malignant lesions delineating them from the surrounding mucosa in the stomach. C2 color enhancement may be more useful for identifying malignant lesions in the stomach and determining their delineation from the surrounding mucosa.

ACKNOWLEDGMENTS

We thank Ms. Hanae Suzuki for her support during this study.

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