Accepted Manuscript online: 2022-11-29 Article published online: 2023-01-19

Differences in color between early gastric cancer and cancer-suspected non-cancerous mucosa on linked color imaging

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submitted 20.3.2022
accepted after revision 13.10.2022
published online 30.11.2022

Bibliography
Endosc Int Open 2023; 11: E90–E96
DOI 10.1055/a-1989-6643
ISSN 2364-3722

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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Supplementary material is available under https://doi.org/10.1055/a-1989-6643

ABSTRACT

Background and study aims Linked color imaging (LCI) can enhance the original color of each area and may useful to detect tumorous lesions during esophagogastroduodenoscopy. However, LCI may also enhance cancer-suspected non-cancerous regional color change. We conducted a retrospective image analysis to investigate the color characteristics of early gastric cancer (EGC) and cancer-suspected non-cancerous mucosa (CSM) in LCI.

Methods LCI images of both EGC and CSM were retrospectively collected from the database of the institution. Fifteen endoscopists individually judged each image as EGC or CSM. The color difference between the inside and outside of the lesions was measured by CIE-Lab analysis in both groups and compared.

Results A total of 245 LCI images of EGC (169) and CSM (76) were extracted and randomly lined for image collection. The test by the endoscopists showed accuracy, sensitivity, and specificity of 64.0 %, 63.7 %, and 64.0 %, respectively. Although the color difference between EGC and CSM was almost the same (12.5 vs. 12.9, not significant), each parameter of ΔL (bright: –0.3 vs. –2.7, P <0.001), Δa (Reddish: 7.2 vs. 9.6, P = 0.004), and Δb (Yellowish: 6.4 vs. 3.8, P <0.001) was significantly different in the groups. The color feature of both positive ΔL and Δb to EGC showed accuracy, sensitivity, and specificity of 54.7 %, 39.6 %, 88.2 %, respectively.

Conclusions The total color difference was almost the same between EGC and CSM; however, their color tones were different on linked color imaging. Although the color characteristics of EGC had high specificity, they also had low sensitivity.

Introduction

Gastric cancer is the fifth most common cancer among cancer-related deaths [1]. Early detection and treatment are essential for preventing death from gastric cancer. Especially when mucosal cancer is detected, cure may be possible with cured by endoscopic treatment, which is minimally invasive and achieves organ preservation [2]. Because patients with early gastric cancer (EGC) are generally asymptomatic, surveillance esophagogastroduodenoscopy (EGD) in high-risk patients or screening EGD during routine health visits is important for early detection and reduction in mortality [3–5]. Because the endoscopic findings for EGC are subtle, it is difficult to identify, not only by endoscopists who are unfamiliar with the diagnosis but also for expert endoscopists [6]. Endoscopists must be particularly careful during EGD to identify slight morphological and color changes that are suspicious for EGC.

The usefulness of image-enhanced endoscopy (IEE), especially narrow band imaging and blue laser imaging, has been widely reported for detection of superficial esophageal and pharyngeal cancers [7, 8]. The IEE technology enhances the color difference between a target lesion and the surrounding mucosa and is beneficial in terms of lesion recognition. The efficacy of IEE for EGC has been reported for diagnosis with magnification [9]. However, the effectiveness for detection of EGC has not been reported in the long period since development of IEE. In 2020, the LCI FIND trial revealed the efficacy of linked color imaging (LCI) for detection of tumorous lesions during EGD [10]. The subanalysis from this study suggested that LCI has a higher detection rate for gastric epithelial lesions compared with white light imaging (WLI). Some reports have described the beneficial color enhancement of EGC compared with the surrounding mucosa in LCI rather than WLI [11, 12], supporting the superiority of LCI over WLI in terms of recognition of tumorous lesions.

Although LCI has a higher detection rate of EGC than WLI, LCI may enhance not only EGC but also the regional color change that is suspicious for EGC. The increase in the number of cancer-suspected non-cancerous mucosa (CSM) leads to unnecessary biopsy or magnified observation, which is time-consuming for patients and endoscopists. According to some reports, each lesion in LCI has a specific hue, such as orange in early-stage gastric cancer and blue-purple in intestinal metaplasia [11–13]. However, the accuracy of attributing such characteristics to specific lesions has not been supported by any data.

In this study, we investigated the color features of EGC and CSM lesions using LCI and aimed to identify their differences while ascertaining the method's accuracy. Moreover, we investigated the relationship between endoscopists' diagnosis and color characteristics of lesions on LCI.

Methods

Creation of image collection

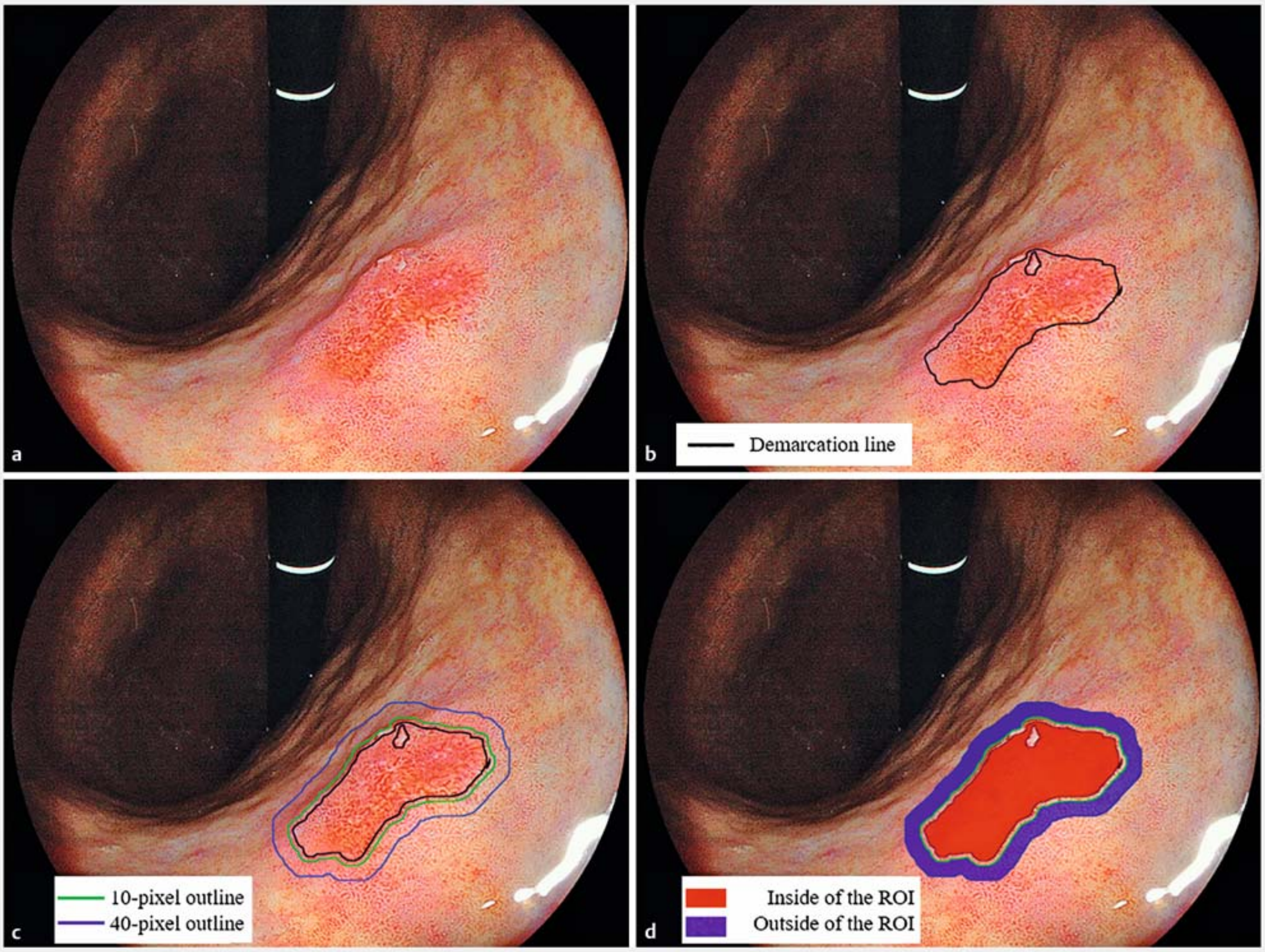
We investigated all EGD cases that were performed using the LASEREO system (EG-L590WR, EG-L590ZW, and EG-L600ZW) equipped with LCI at the Okayama University Hospital between January 2014 and December 2018. All EGD procedures were performed by an expert endoscopist or young endoscopist under the supervision of an expert. Because this was a retrospective study, the EGD procedure could not be regulated. Patients that did not undergo biopsy were excluded. Based on the purpose of biopsy and histological findings, EGC and CSM were collected. EGC were cases that underwent endoscopic resection and were histologically diagnosed as mucosal or slightly invasive submucosal carcinoma (< 500 μm). Cases were designated as CSM when endoscopists performed biopsies because of suspicion for or to rule out EGC, but histological examination revealed the presence of non-cancerous tissue. We excluded cases without a proper LCI image of the target lesion, protruded-type lesions, and lesions > 30 mm in size in both the EGC and CSM groups. We also excluded cases of poorly differentiated type in the EGC group, because the color was vastly different from differentiated adenocarcinoma [14–16]. Similarly, cases of white-toned lesions that were biopsied for suspicion of poorly differentiated lesions were excluded from the CSM group. One LCI image of the lesion focused in the middle range was extracted from these cases by an expert endoscopist (H. K.). Image collection was performed using randomly lined EGC and CSM images. The following data from the included cases were collected from patient medical records for analysis of lesion characteristics: age, sex, *Helicobacter pylori* status, degree of atrophic gastritis, location of the target lesion, estimated lesion size, invasion depth in EGC, and morphology.

Test of the image collection by endoscopists

The image collection, which consisted of randomly lined LCI images of EGC and CSM, was tested by 15 endoscopists who routinely used LCI, except for those who created the image collection (H.K.). All endoscopists were informed that there was a lesion of EGC or CSM per LCI image, but the total number of each EGC and CSM was not provided. The test was conducted by each individual without a time limit. The questions that needed to be answered included whether the image depicted EGC or CSM and which factors mainly contributed to the diagnosis, color or morphological finding. The diagnoses were made at endoscopist discretion and as per their experience. The factor contributing to the diagnosis was indicated by a numerical rating scale (NLR) of 1 to 5. The NLR score was as follows: 1, mostly diagnosed by color; 2, color more beneficial than morphology; 3, Even; 4, morphology more beneficial than color; and 5, mostly diagnosed by morphology. We defined "cases judged by color" as over half of the answer was judged by the color of score 1 or 2, whether the answer was correct or not. Similarly, "cases judged by the morphology" were defined as over half of the answers were judged by the morphology of score 4 or 5.

Color measurement methods

Color processing and analysis were performed using Adobe Photoshop CC (Adobe Systems Inc., San Jose, California, United States). The algorithm used to locate the region of interest (ROI) in the selected image is shown in ▶ **Fig. 1**. Because the color of the background mucosa was slightly different in each patient, we measured the color difference between the inside and outside of the ROI. A demarcation line was drawn by one endoscopist (H.K.) for all images, in reference to the histological examination of the ESD-resected tissue in the EGC group and uniformly colored area with biopsied points in the CSM group. In addition, two lines around the demarcation line were drawn with an extension of 10 pixels and 40 pixels, using Photoshop's range selection extension function, and the area surrounded by these two lines was defined as outside of the ROI.



► **Fig. 1** Image processing protocol for color analysis. **a** Linked color image of early gastric cancer (EGC) or cancer-suspected non-cancerous mucosa (CSM) was prepared. **b** Demarcation line was drawn in reference to the histological examination of the ESD-resected tissue in the EGC group and color uniform area with biopsied points in the CSM group. Unusually colored areas, such as light reflections, scopes, and blood, were partially excluded from the demarcation line. **c** Two lines around the demarcation line were drawn with an extension of 10 pixels and 40 pixels using Photoshop's range selection extension function. **d** The area inside the demarcation line was defined as the inside of the region of interest (ROI) and outside of the ROI was defined as surrounded by 10-pizel and 40pixel lines, which were expanded from demarcation line. A line of extended 10 pixels from the demarcation line was created to exclude the uncertain area that comes from the handmade line by a single endoscopist.

A line that extended 10 pixels from the demarcation line was created to exclude the uncertain area that came from the handmade line by a single endoscopist. Unusually colored areas such as light reflections, scopes, and blood were partially excluded from the ROI. The color values were calculated using CIE-Lab color space (CIE: Commission Internationale d' Eclairage) developed by the International Commission on Illumination in 1976 [17]. The color value was expressed using the three-dimensional color parameters L* (black to white; range, 0 to + 100), a* (green to red; range, −128 to + 127), and b* (blue to yellow; −128 to + 127). A positive value represents a shift toward white in axis L*, red in a*, and yellow in axis b*, indicating all colors visible to the human eye [18, 19]. The median ([L*inside, a*inside, b*inside] and [L*outside, a*outside, b*outside]) of the color values in the ROI and outside of the ROI, respectively, were measured. The color differences of L*, a*, and b* were also described as ΔL, Δa, and Δb. These parameters were calculated using the following equations:

$\Delta L = L^{*}\text{inside} - L^{*}\text{outside}$

$\Delta a = a^{*}\text{inside} - a^{*}\text{outside}$

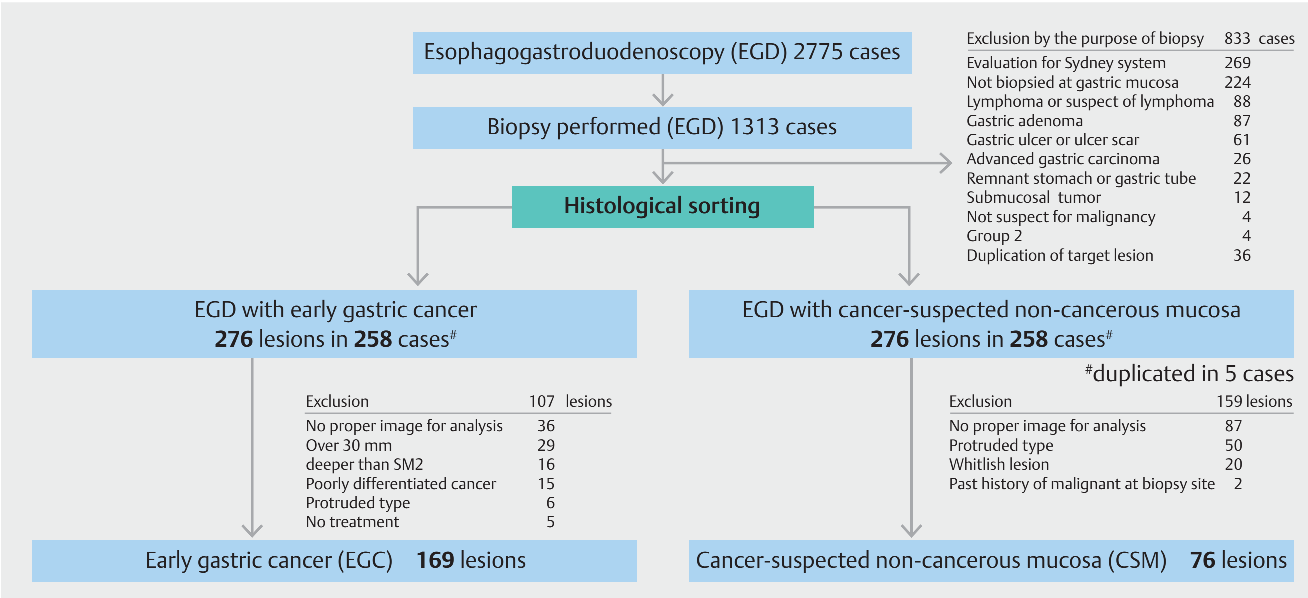
$\Delta b = b^{*}\text{inside} - b^{*}\text{outside}$

The total color difference between the inside and outside of the lesion, ΔE, was calculated using the following formula:

$\Delta E = \sqrt{}(L^{*}\text{inside} - L^{*}\text{outside})^2 + (a^{*}\text{inside} - a^{*}\text{outside})^2 + (b^{*}\text{inside-}\ b^{*}\text{outside})^2$

Statistics

All statistical analyses were performed using JMP PRO (ver. 15; SAS Institute Inc., Cary, North Carolina, United States). All continuous variables were expressed as medians with ranges or percentages. The color difference between EGC and CSM was compared using the Wilcoxon signed-rank test. Receiver oper-



▶ **Fig. 2** Image collection flow.

ating characteristic (ROC) curve analysis was performed to evaluate the detection ability of EGC for each color parameter. Statistical significance was set at $P < 0.05$.

Results

During the inclusion period, 2,775 cases of EGD were performed using the LASEREO system and the applicable scope. Based on the inclusion and exclusion criteria, 245 LCI images (EGC, 169; CSM, 76) with target lesions were extracted (▶ **Fig. 2**). The image collection was created using randomly arranged EGC and CSM images. Baseline characteristics of patients are shown in ▶ **Table 1**.

Testing of the image collection by the 15 endoscopists showed accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 64.0 %, 63.7 %, 64.0 %, 82.2 %, and 48.4 %, respectively. The "cases judged by the color" were 65 (39 %) and 24 (30 %) and "cases judged by the morphology" were 104 (61 %) and 55 (70 %) in the EGC and CSM groups, respectively. The accuracy, sensitivity, specificity, PPV, and NPV of "cases judged by the color" and "cases judged by the morphology" were almost the same.

The color difference (ΔE) was almost the same for EGC and CSM (12.5 vs. 12.9 %, not significant, ▶ **Table 2**). However, there was a clear difference in the content of color differences. Although EGC had significantly higher ΔL and Δb and lower Δa compared with CSM, the plot of each parameter showed overlapping of colors between EGC and CSM (Supplementary Fig. 1). The area under the curve (AUC) for discrimination of EGC and CSM in ΔE, ΔL, Δa, and Δb was 0.54, 0.70, 0.61, and 0.63, respectively (Supplemental Fig. 2).

Because the single parameter of color difference could not distinguish EGC and CSM, a combination of parameters was attempted to determine the specific color. Although the value of Δa was significantly higher for CSM than for EGC, 221 of the 245 cases (90.2 %) had positive values and overlapped significantly. Therefore, it was difficult to distinguish EGC and CSM in combination with Δa. Therefore, a two-dimensional plot was con-

▶ **Table 1** Characteristics of patients and target lesions.

	EGC	**CSM**
Number	169	79
M/F	125/44	58/21
age	75 (49–9)	70 (38–83)
Helicobacter pylori status		
▪ non-infection/past/present/unknown	1/132/36/0	4/62/13/5
Atrophic gastritis		
▪ none/mild/moderate/severe	1/14/57/97	4/15/38/22
Location		
▪ UM/L	109/60	47/32
Estimated lesion size	11 (2–30)	8 (3–20)
invasion depth		
▪ M/SM1	152/17	
Morphology		
▪ Superficial depressed/flat/superficial protruded	125/7/37	69/7/3

EGC, early gastric cancer; CSM, cancer-suspected non-cancerous mucosa; M, male; F, female; UM, upper and middle third of the stomach; L, lower third of the stomach; M, mucosal carcinoma; SM1, slightly invasive submucosal carcinoma (< 500 μm)

▶ **Table 2** Color difference between the region of interest and surrounding mucosa in early gastric cancer and cancer-suspected non-cancerous mucosa.

	EGC (n = 169)	CSM (n = 79)	*P* value
ΔE	12.5	12.9	n.s
ΔL	−0.3	-2.7	< 0.001
Δa	7.2	9.6	0.004
Δb	6.4	3.8	< 0.001

EGC, early gastric cancer; CSM, cancer-suspected non-cancerous mucosa.

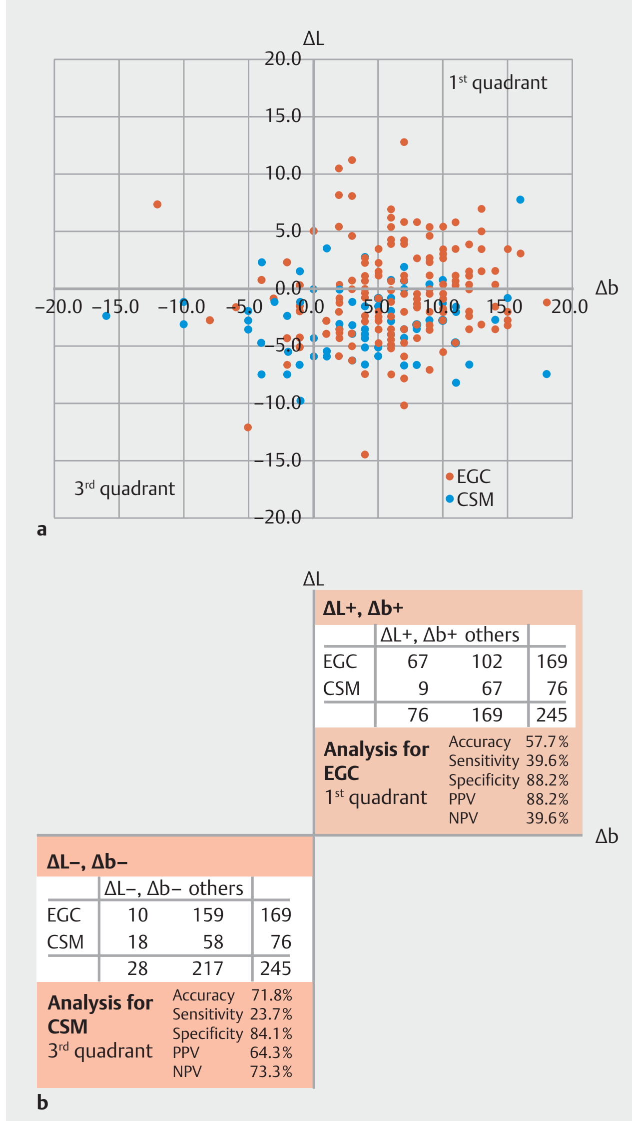
structed for ΔL and Δb (▶ **Fig. 3**). The accuracy, sensitivity, specificity, PPV, and NPV for diagnosing EGC at the first quadrant, which had positive values in both ΔL and Δb, were 54.7 %, 39.6%, 88.2 %, 88,2 %, and 39.6 %, respectively. The diagnostic accuracy was worse than the endoscopist test but exhibited high specificity (▶ **Table 3**). Meanwhile, in the area of the third quadrant, which had negative ΔL and Δb values, the accuracy, sensitivity, PPV, and NPV for CSM were 71.8 %, 23.7 %, 94.1 %, 64.3 %, and 73.3 %, respectively.

Discussion

LCI could enhance the color of EGC and highlight it among the surrounding mucosa [11, 12], which might contribute to the higher detection rate of EGC than with WLI [10]. However, the color enhancement technology might also show an increase in suspicious areas, especially in cases of chronic atrophic gastritis, which has many localized unevenly colored areas. In this study, ΔE between the inside and outside of the ROI was similarly high in EGC and CSM, and there was no significant difference between them. This indicates that EGC and CSM are equally recognized by endoscopists in terms of the color difference between the lesion and the surrounding mucosa. However, the color components were significantly different between the groups. EGC had higher ΔL and Δb and lower Δa than the CSM. The different color features between EGC and CSM may help endoscopists distinguish them.

Although the median ΔL, Δa, and Δb between EGC and CSM were significantly different, these parameters overlapped in most cases. Therefore, it may be difficult to judge them using only a single parameter of color difference. As for Δa, most cases had positive values for EGC and CSM (Supplementary Fig. 1). Therefore, red was a color indicative of cancer but not specific to EGC. The combination of positive values in both ΔL and Δb represented high specificity for EGC, and negative values for both ΔL and Δb depicted a high specificity for CSM. Although the sensitivity was low, the high specificity indicated the specific color of each EGC and CSM in LCI. Overall, compared to the surrounding mucosa, the colors of EGC and CSM were bright reddish yellow (called orange) for EGC and a dark reddish blue (called blue-purple) for CSM (▶ **Fig. 4**).

The results of the survey by the endoscopists were not as good, given the accuracy, sensitivity, specificity, PPV, and NPV



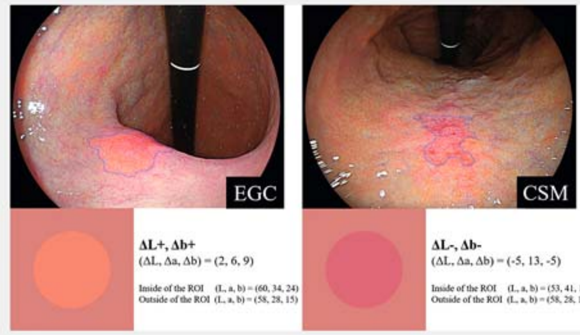
▶ **Fig. 3** Plot on the ΔL and Δb dimension. **a** Plot of all cases on ΔL and Δb dimensions. Many of the cases in the area of the first quadrant, which had positive scores for both ΔL and Δb, were EGC. **b** The accuracy, sensitivity, specificity, PPV and NPV for EGC in the 1st quadrant, which had both positive ΔL and Δb values, were 54.7 %, 39.6 %, 88.2 %, 88.2 %, and 39.6 %, respectively. In contrast, many of the cases in the area of the third quadrant, which had negative scores for both ΔL and Δb, were CSM. The accuracy, sensitivity, specificity, PPV and NPV for CSM were 71.8 %, 23.7 %, 94.1 %, 64.3 %, and 73.3 %, respectively. EGC, early gastric cancer; CSM, cancer-suspected non-cancerous mucosa; PPV, positive predictive value; NPV, negative predictive value.

of 64.0 %, 63.7 %, 64.0 %, 82.2 %, and 48.4 %, respectively. The reasons for this low accuracy may come from the inclusion criteria for CSM, which were clinically suspected carcinoma that underwent biopsy. The images of the CSM were very similar to those of the EGCs. Moreover, this image collection consisted of only a single LCI image per lesion, and it was difficult to accurately diagnose EGC or CSM even for an experienced endoscopist. The accuracy and sensitivity in diagnosing EGC

▶ **Table 3** Diagnostic accuracy for EGC by color feature and endoscopist's test.

	Color feature	Endoscopist's test		
	ΔL, Δb > 0	All	Major finding contributing to diagnosis	
			Color	Morphology
Number of images (%)	248	248	89 (36)	159 (64)
EGC (%)	169	169	65 (39)	104 (61)
CSM (%)	79	79	24 (30)	55 (70)
Accuracy, %	54.7	64.0	64.0	63.9
Sensitivity, %	39.6	63.7	64.6	63.3
Specificity, %	88.2	64.0	63.1	65.3
PPV, %	88.2	82.2	84.8	80.6
NPV, %	39.6	48.4	42.0	51.8

EGC, early gastric cancer; CSM, cancer-suspected non-cancerous mucosa; PPV, positive predictive value; NPV, negative predictive value.



▶ **Fig. 4** Typical cases of each EGC and CSM and color samples. The EGC case had positive ΔL, Δa, and Δb scores, representing a bright reddish and yellowish color compared to the surrounding mucosa. The CSM case had high Δa, but negative scores of ΔL and Δb, representing the reddish but dark bluish color compared with the surrounding mucosa. EGC, early gastric cancer; CSM, cancer-suspected non-cancerous mucosa.

using the color features, and positive ΔL and Δb values were not superior to the endoscopist data. As shown in the endoscopist test, the major finding that contributed to the diagnosis was morphology, not color. The attempt to diagnose EGC or CSM solely based on color was disadvantageous. However, the color characteristics of the lesions corresponding to positive and negative ΔL and Δb values were highly specific for EGC and CSM. The knowledge of these color characteristics may improve the confidence level of endoscopists for identifying EGC or CSM without magnification. On the other hand, endoscopists should be aware that these color features are not highly sensitive. Some previous reports have described the unique colors indicative of lesions of EGC and gastric intestinal metaplasia [11–13]; however, even though these color characteristics were highly specific, they exhibited low sensitivity in this study. Endoscopists should be aware that many EGC lesions lack a distinctive color and that judging the lesion as non-cancerous solely based on color tones would be dangerous.

The parameter of ΔL representing brightness was excluded in past color evaluation studies, including our previous report [11], because ΔL varies depending on light exposure and distance from the endoscope. However, there was a clear difference in ΔL between EGC and CSM. The value of ΔL varies greatly depending based on photo conditions; however, the Δa and Δb values also vary according to the situation. In the CIE-Lab color evaluation, brightness and saturation are major factors, and they cannot be easily removed in color analysis. The results of this study with a large number of cases show that ΔL is also a major factor in recognizing the specific color of EGC and CSM.

Most of the histological evaluations of CSM included intestinal metaplasia. There have been reports of patchy distribution of atrophy and intestinal metaplasia in chronic atrophic gastritis [20, 21]. In this study, localized intestinal metaplasia tended to be biopsied as CSM because of its different coloration and morphology compared with the surrounding mucosa. Intestinal metaplasia has been reported to be a lavender color in LCI [13], which is a reddish dark blue color. In this study, the specific color of CSM was reddish dark blue compared to the surrounding mucosa. Even if there is a regional color area with such a color, it may not be cancer but intestinal metaplasia.

This study had some limitations. First, a single endoscopist collected all the images, and many cases were excluded because of photo conditions. All candidate images were checked, but this may have resulted in selection bias. However, the low accuracy of the results of the endoscopist survey show the similarity of EGC and CSM in this image collection. Even using such an image collection, we could identify the color characteristics of both EGC and CSM by color analysis, which was completely objective data. Second, the value of the color difference was simply the objective data. It is not known whether endoscopists can recognize them during examinations. However, knowledge about color features can aid an endoscopist's judgement in a clinical setting. Third, the exclusion of undifferentiated-type EGC may have reduced the clinical value of this study. However, many reports have revealed that undifferentiated-type EGC lesions are pale-colored, which is clearly different from differentiated-type EGC [14–16]. Mixing the different lesions with varying color characteristics may have led to confusion and an erroneous result. Also, the small number of undifferentiated-type EGC cases prevented their subanalysis. Lastly, we could not investigate the comparison with white light images that were used for surveillance endoscopy in usual institutions. Surely, there were stored images of WLI; however, the number cases with a set of reviewable clear images of LCI and WLI was very small. For comparison with WLI, a prospective study is needed to collect the appropriate images.

Conclusions

Although the total color difference was almost the same between EGC and CSM, they had different color tones on LCI. The specific color of EGC was bright, reddish yellow, and that of the CSM was dark, reddish blue. Awareness of these specific color characteristics may improve the confidence level of endoscopists in identifying EGC or CSM without magnification; however, they should also be aware of the low sensitivity of these color characteristics.

Acknowledgments

The authors thank Yuka Obayashi, Yuki Okamoto, Yuki Baba, Hiroyuki Sakae, Makoto Abe, Shunpei Yamamoto, Masayasu Omori, Yasushi Yamasaki, Hideaki Kinugasa, and Keita Harada for their contribution to the image evaluation test.

Competing interests

The authors declare that they have no conflict of interest.

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