

[ ORIGINAL ARTICLE ]

## Linked-color Imaging May Help Improve the Visibility of Superficial Barrett's Esophageal Adenocarcinoma by Increasing the Color Difference

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### Abstract:

**Objective** Linked-color imaging (LCI), a new technology for image-enhanced endoscopy, emphasizes the color of the mucosa, and its practicality in the detection of early gastric and colon cancers has been reported. However, whether or not LCI is useful for the diagnosis of Barrett's adenocarcinoma (BA) has been unclear. In this study, we explored whether or not LCI enhances the color difference between a BA lesion and the surrounding mucosa.

**Methods** Twenty-one lesions from 20 consecutive patients with superficial BA who underwent endoscopic submucosal dissection between November 2014 and September 2017 were retrospectively examined. The color differences ( $\Delta E^*$ ) between the inside and outside of the lesion were evaluated retrospectively using white-light imaging (WLI), blue-light imaging (BLI), and LCI objectively, based on a Commission Internationale de l'Eclairage (CIE) lab color system. Furthermore, we compared the morphology, color, and circumferential location of the lesion.

**Results** The median values of the color difference ( $\Delta E^*$ ) in WLI and BLI were 9.1 and 5.8, respectively, and no difference was observed. In LCI, the median color difference was 17.6, which was higher than that of WLI and BLI. Regardless of the morphology, color, and circumferential location of BA lesions, the color difference was larger in LCI than in WLI.

**Conclusion** LCI increases the color difference between the BA and the surrounding Barrett's mucosa.

**Key words:** Barrett's adenocarcinoma, Barrett's esophagus, blue-light imaging, linked color imaging, color difference

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### Introduction

The incidence of Barrett's adenocarcinoma (BA) has remarkably increased 3- to 6-fold in the past 20 to 40 years in Western countries and is becoming more common in Japan with time (1-5). BA is associated with a poor prognosis due to high rates of metastasis when detected at an advanced stage (6). However, for superficial BA, endoscopic resection

can be performed, for which a favorable long-term prognosis has been reported (7, 8). Therefore, it is necessary to detect BA in the early stages, and proper surveillance of Barrett's esophagus (BE) is crucial.

In Western countries, the Seattle Protocol with a random biopsy is recommended for the surveillance of BA (9). The current gold-standard technique for detecting BA in a surveillance program involves quadratic esophageal biopsies every 2 cm during endoscopy. A random biopsy is neces-

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sary, as only 13% of dysplastic changes are visible nodules (10). However, a random biopsy is invasive and costly; therefore, in practice, only 50% of surveillance endoscopies are estimated to follow this method (11). In Japan, the most common and efficient way to detect BA early is via a detailed endoscopic examination with a targeted biopsy. However, the endoscopic diagnosis of superficial BA is complicated. A simple surveillance method using new endoscopic technology is therefore needed (12).

Image enhancement endoscopy (IEE) is able to emphasize the color and structure of cancerous lesions. Blue-light imaging (BLI) and linked-color imaging (LCI) are IEE techniques that can be applied to the LASEREO<sup>®</sup> system. LCI enhances colors so that reddish colors are redder and whitish colors are whiter. LCI is an image-enhanced endoscopy system that facilitates the diagnosis of cancer and inflammation by emphasizing subtle color differences in the mucosa. LCI increases the color difference between lesions and the surrounding mucosa compared to white-light imaging (WLI). Another advantage of LCI is that the visibility of the surface layer of the mucosa, which is obtained at a short wavelength of BLI light, is improved (13-16). LCI reportedly improves the visibility during screening of early cancerous lesions in the stomach and colon (17-22). We expect LCI to also be useful for detecting superficial BA, but whether or not LCI is actually effective for the diagnosis of superficial BA is unclear at present.

We therefore investigated whether or not LCI increased the color difference, which may contribute to visibility, during superficial BA screening.

## Materials and Methods

### Patients

Twenty-one lesions from 20 consecutive patients with superficial BA who underwent endoscopic submucosal dissection (ESD) in our hospital between November 2014 and September 2017 were included in this study. The study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine, Sendai, Japan.

The *Helicobacter pylori* (HP) infection status of the patients was evaluated by a histological assessment (Giemsa staining) of gastric biopsies from the antrum and body as well as a serum IgG antibody to HP test (E Plate "Eiken" *H. pylori* antibody; Eiken Chemical, Tokyo, Japan). We considered the patients to be HP-negative when both tests were negative and as HP-positive when at least one test was positive. The patients were also examined to determine whether or not they were taking proton pump inhibitors (PPIs) or potassium-competitive acid blockers (P-CABs) at the time of their first visit to our hospital. The pathological depth of the target lesions after ESD was also examined.

### Esophagogastroduodenoscopy (EGD)

EGD was performed using a high-definition EG-L600WR

or EG-L600ZW endoscope corresponding to the LASEREO<sup>®</sup> endoscopic system (FUJIFILM, Tokyo, Japan) before the endoscopic treatment. The WLI, BLI, and LCI images of the targeted cases recorded in the filing system were extracted and retrospectively evaluated using a computer to measure the color difference. The color difference between the inside and outside of the BA lesion was examined using endoscopic images taken from almost the same position on the captured image in a fully extended condition without magnification.

### Endoscopic findings

The following presented endoscopic findings of the lesions were evaluated by two experts certified by the Japan Gastroenterological Endoscopy Society. The esophagogastric junction (EGJ) was endoscopically defined as the lower margin of palisading small vessels according to the Japanese Classification of Esophageal Cancer, 11th Edition (23, 24). If the palisading small vessels were unclear, the oral margin of the longitudinal folds of the greater curvature of the stomach was defined as the EGJ (23, 24). Patients who were diagnosed with Barrett's mucosa extending longitudinally for  $\geq 3$  cm were sub-grouped as long-segment BE (LSBE), and those who were diagnosed with Barrett's mucosa extending  $< 3$  cm from the EGJ were sub-grouped as short-segment BE (SSBE) (23, 24). In this study, BA was defined as the presence of peculiar esophageal glands at the submucosa of the lesion histologically and/or Barrett's epithelium on the anal side of the lesion on upper gastrointestinal endoscopy. The lesion diameter was measured endoscopically and pathologically. The macroscopic form was diagnosed endoscopically and classified as the protruding type or flat to depressed type. All cases were confirmed to be superficial cancer based on the final pathological diagnosis.

### An objective evaluation using the CIE Lab color space

The color difference between the lesion and the surrounding mucosa was evaluated numerically using the  $L^*a^*b^*$  color space. The  $L^*a^*b^*$  color space is currently the most commonly used color system in all fields for representing the color of an object. In the  $L^*a^*b^*$  color space, lightness is represented by  $L^*$ , and  $a^*$  and  $b^*$  indicate the color direction ( $a^*$  indicates the red direction,  $-a^*$  indicates the green direction,  $b^*$  indicates the yellow direction, and  $-b^*$  indicates the blue direction). Since colors are quantified in the  $L^*a^*b^*$  color space, the color difference ( $\Delta E^*$ ) between colors can also be quantified and expressed (19, 21, 25-29).

The target region of interest (ROI) area for measuring the color difference was selected from the BA lesion and the surrounding Barrett's mucosa by two endoscopic specialists. The target ROI area in the non-cancerous surrounding BA was selected by the following criteria: 1) Barrett's mucosa just outside and adjacent to the BA lesion and 2) within the ESD resection range, and 3) the ROI area not containing squamous epithelium or squamous epithelial islands. The

ROI selected from non-cancerous mucosa was confirmed to be non-cancerous pathologically based on ESD specimens. In addition, the presence or absence of specialized intestinal metaplasia (SIM) was examined in ESD specimens for the ROI regions selected from non-cancerous mucosa.

The ROI area consisted of 2,500 pixels (50×50 pixels). The average of the absolute color values ( $L$ ,  $a$ ,  $b$ ) in the ROI was calculated from the histogram panel using an image analysis software program (Adobe Photoshop CC<sup>®</sup> 2017; Adobe Systems, San Jose, USA).  $L$ ,  $a$ , and  $b$  are color values in the  $Lab$  color unit of Photoshop. The  $L$ ,  $a$ , and  $b$  color values were transformed into  $L^*a^*b^*$  color values in CIE Lab, as follows:  $L^*=L/256 \times 100$ ,  $a^*=a-128$ , and  $b^*=b-128$  (25-28). To evaluate the color differences, the color value of the objective lesion was assessed based on  $L^*a^*b^*$  ( $L^*$ =light/dark;  $a^*$ =red/green; and  $b^*$ =yellow/blue) color values in the CIE Lab color space system. The color differences of the value in the  $L^*a^*b^*$  color spaces were calculated [ $\Delta E^* = ((\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2)^{1/2}$ ] (25, 26). The color differences ( $\Delta E^*$ ) within the ROI between BA and the surrounding Barrett's mucosa on WLI, BLI, and LCI were compared and evaluated. In addition,  $\Delta L^*$  (difference in  $L^*$  value indicating brightness),  $\Delta a^*$  (difference in  $a^*$  value),  $\Delta b^*$  (difference in  $b^*$  value), and  $\Delta C^*$  (difference in saturation;  $\Delta C^* = [(a_{BA}^*)^2 + (b_{BA}^*)^2]^{1/2} - [(a_{BE}^*)^2 + (b_{BE}^*)^2]^{1/2}$ ;  $a_{BA}^*$  is  $a^*$  in BA Lesion,  $b_{BA}^*$  is  $b^*$  in BA Lesion,  $a_{BE}^*$  is  $a^*$  in BE, and  $b_{BE}^*$  is  $b^*$  in BE) were also calculated. The  $\Delta L^*$ ,  $\Delta a^*$ ,  $\Delta b^*$ , and  $\Delta C^*$  on WLI, BLI, and LCI were then compared.

### Statistical analyses

Data management and statistical analyses were performed using the JMP<sup>®</sup> 14.1.0 software program (SAS Institute, Cary, USA). The results in the present study are expressed as median values. Wilcoxon's signed-rank test was used to compare the parameters between any combination of two groups. Categorical variables in the patients' backgrounds were compared using Fisher's exact test. A  $p$  value of  $<0.05$  was considered statistically significant.

## Results

All 20 cases were men, and 1 had double lesions (Table 1). The median age was 66.5 years old, and the median body mass index (BMI) was 24.8. The number of SSBE cases was 16 (80%). HP infection was positive in 4 cases, negative in 15 cases, and negative after eradication in 1 case. Seven of the 20 patients (8 of 21 lesions) were taking PPIs or P-CABs. Regarding the circumferential location of the 21 lesions, 17 (80.9%) were located in the 0-3 o'clock direction, and the remaining 4 (19.1%) were found in the other directions. The median diameter of the lesions was 14.0 mm. Regarding the color of the lesions, 18 (85.7%) had redness, and 3 had a similar color to the surrounding tissue or were discolored. Nine lesions (42.9%) were protruding, and 12 lesions (57.1%) were flat or depressed. The pathological depth of the 21 target lesions after ESD was

the superficial muscularis mucosae (SMM) in 5 cases, lamina propria mucosae (LPM) in 2 cases, deep muscularis mucosae (DMM) in 9 cases, and submucosa (SM) in 5 cases. Of the 5 lesions in the SM, 2 were in SM1, and 3 were in SM2 (SM1 was the upper layer of the submucosa [ $<200 \mu\text{m}$ ]) (Table 1).

The median value of the color difference on WLI between the lesion part and the surrounding Barrett's mucosa in the targeted 21 BA cases was 9.1. In IEE, the median color difference on BLI was 5.8, showing no significant difference from WLI ( $p=0.138$ ). However, the median color difference on LCI was 17.6, which was higher than that on WLI or BLI ( $p<0.001$ ,  $p<0.001$ , respectively) (Fig. 1). The observation method with the largest color difference was LCI in 18 of 21 lesions. Among the 17 SSBE lesions, 13 (76.4%) had the largest color difference in LCI. In 4 cases of LSBE, the color difference was the strongest in LCI in all cases. The  $\Delta L^*$  did not differ markedly between WLI and LCI ( $p=0.75$ ). The  $\Delta C^*$  was higher in the LCI group than in the WLI group ( $p<0.001$ ). The  $\Delta b^*$  showed no marked difference between WLI and LCI ( $p=0.398$ ). However, the  $\Delta a^*$  was higher in LCI than in WLI ( $p<0.0001$ ) (Table 2).

Among the 18 reddish lesions, 15 (83.3%) showed a greater color difference on LCI than in WLI and BLI. In 3 lesions with a similar color to the surrounding mucosa or discolored, LCI also showed a greater color difference than WLI or BLI (Table 3). The color difference in the protruding type was greater with LCI than with WLI or BLI ( $p<0.05$ ,  $p<0.05$ , respectively), although no significant difference was found between WLI and BLI. In addition, the color difference in flat to depressed lesions was greater with LCI than with WLI or BLI ( $p<0.01$ ,  $p<0.001$ , respectively). There was no significant difference between WLI or BLI. The color difference was increased in LCI regardless of the morphology of the lesion (Fig. 1). Regarding the relationship between the circumferential location of the BA lesions and the color difference, among the 17 lesions in the 0-3 o'clock direction, LCI showed the greatest color difference in 14 cases (82.4%). In addition, among the 4 lesions in directions other than the 0-3 o'clock direction, the color difference was the greatest in LCI among all cases (Table 3).

In addition, SIM was present at the location of the ROI outside the lesion in 3 of the 21 lesions. In the other 18 lesions, no SIM was found at the location of the ROI. The 3 lesions that showed SIM in the ROI site all had the largest color difference on LCI, and of the 18 lesions that did not show SIM, the color difference was also largest on LCI in 15 cases. Regarding the remaining three cases, two showed the largest color difference on WLI, and one showed the largest difference on BLI. With or without SIM, the color difference was larger in most cases on LCI.

## Discussion

The present study confirmed that LCI increased the color difference between the BA lesion and the surrounding Bar-

**Table 1. The Backgrounds and Characteristics.**

Total patients (n=20 )			
Age, years, median (IQR)		66.5	(13.3)
Sex, n	male	20	(100%)
BMI, median (IQR)		24.8	(3.2)
Barrett's mucosa for background, n	SSBE	16	(80%)
<i>H.pylori</i> infection, n			(4/15/1)
(positive/negative/after eradication)			
Oral intake of PPI or P-CAB, n		7	(35%)
Total lesions (n=21 )			
Circumferential location, n	0-3 o'clock direction	17	(80.9%)
Color of lesions, n	reddish	18	(85.7%)
	discolored	3	(14.3%)
Form of lesions, n	0-I	3	(14.3%)
	0-IIa	5	(23.8%)
	0-IIa+IIc	1	(4.8%)
	0-IIb	2	(9.5%)
	0-IIc	10	(47.6%)
Depth of lesions, n	SMM	5	(23.8%)
	LPM	2	(9.5%)
	DMM	9	(42.9%)
	SM1	2	(9.5%)
	SM2	3	(14.3%)
The diameter of the lesions, mm, median (IQR)		14	(11)

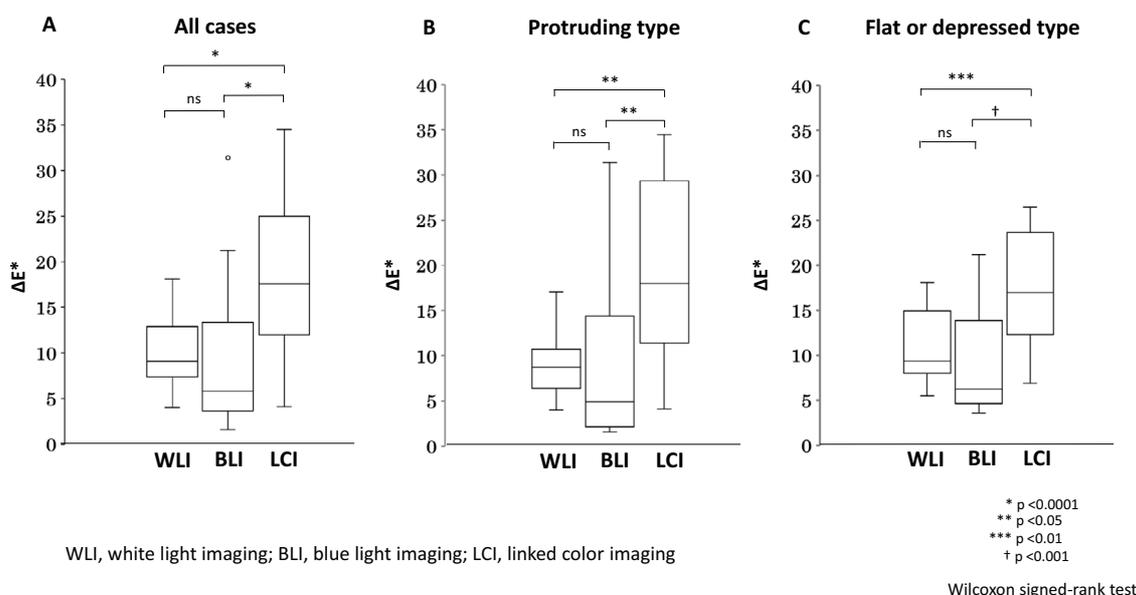
IQR: interquartile range, BMI: body mass index, SSBE: short segment Barrett's esophagus, PPI: proton pump inhibitor, P-CAB: potassium-competitive acid blocker, SMM: superficial muscularis mucosae, LPM: lamina propria mucosae, DMM: deep muscularis mucosae, SM: submucosa

rett's mucosa. It was shown that the color difference was greatest on LCI observation in more than 80% of the cases, suggesting that LCI objectively contributes to improving the color difference between superficial BA and the surrounding mucosa.

On BLI and LCI with the LASEREO<sup>®</sup> system using Fuji-film's laser light source, the light with a wavelength of 440 to 460 nm reflected in the deeper structure of the mucosa and BLI light with a wavelength of 400 to 420 nm reflected in the blood vessel structure of the mucosal surface layer and the microscopic mucosal surface structures are dimmed. Furthermore, LCI light is color-processed on the obtained image (13-16). Advantages of LCI mode include the fact that the visibility of the mucosal surface layer, which is obtained at a short wavelength of BLI light, is included with this approach, and color processing is also performed computationally to improve the visibility. Taken together, these factors enhance the visibility of the lesion by increasing the color difference (13-15), thus making it possible to distinguish the lesion from the surrounding mucosa. The utility of LCI for the surveillance of cancer by increasing the color difference was previously demonstrated in gastric and colon

cancer (16-22). A previous study reported that LCI also improved the visibility of SSBE in the esophagus (29). However, whether or not LCI improves the visibility for superficial BA has been unclear. In this study, LCI was shown to increase the color difference in BA lesions for the first time.

The color difference is composed of  $\Delta L^*$ ,  $\Delta a^*$ , and  $\Delta b^*$ , and there was a significant difference in color difference between WLI and LCI, but there was no difference in  $\Delta L^*$  (indicating brightness). In contrast, the  $\Delta C^*$  (reflecting the difference in saturation) was larger with LCI than with WLI. Therefore, visibility may be improved due to the increased saturation with LCI. There was no marked difference in the  $\Delta b^*$  between WLI and LCI, but the  $\Delta a^*$  was significantly larger with LCI than with WLI. As the  $a^*$  increases in the positive direction, the redness increases, and as it increases in the negative direction, the greenness increases. LCI increased both the  $a^*$  in the red-green component and  $b^*$  in the yellow-blue component (18). In the present study, LCI showed significant color differences, mainly by increasing the saturation ( $\Delta C^*$ ). Among the elements of  $a^*$  and  $b^*$ , LCI had a higher  $a^*$  value at the BA lesion than WLI. The differences in color ( $\Delta E^*$ ) and saturation ( $\Delta C^*$ ) on LCI be-



**Figure 1.** A comparison of the color difference ( $\Delta E^*$ ) based on the  $L^*a^*b^*$  color spaces. Box plots of the color difference. Small circles indicate outliers. (A) Color differences between Barrett's adenocarcinoma and Barrett's esophagus in all cases. Statistically significant differences were observed between WLI and LCI and between BLI and LCI. No significant difference was observed between WLI and BLI. (B) Color differences between Barrett's adenocarcinoma and Barrett's esophagus in the protruding lesion. Statistically significant differences were observed between WLI and LCI and between BLI and LCI. No significant difference was observed between WLI and BLI. (C) Color differences between Barrett's adenocarcinoma and Barrett's esophagus in flat or depressed lesions. Statistically significant differences were observed between WLI and LCI and between BLI and LCI. No significant difference was observed between WLI and BLI. \* $p < 0.0001$ , \*\* $p < 0.05$ , \*\*\* $p < 0.01$ , † $p < 0.001$ . ns: not significant

**Table 2.** Comparison of the Color Differences between BA and the Surrounding BE Mucosa with WLI and LCI.

	WLI	LCI	p value
Total lesions (n=21)			
$\Delta E^*$	9.1 (3.7)	17.6 (12.5)	<0.0001
$\Delta C^*$	6.4 (4.1)	13.8 (14.4)	<0.001
$\Delta L^*$	-0.4 (9.2)	-0.7 (8.7)	0.75
absolute value ( $L^*$ )			
BA lesion	36.2 (9.1)	45.5 (12.7)	
surrounding BE	39.9 (10.7)	47.3 (8.1)	
$\Delta a^*$	5.3 (3.8)	11.4 (10.5)	<0.0001
absolute value ( $a^*$ )			
BA lesion	30.8 (11.4)	39.3 (15.4)	
surrounding BE	28.4 (11.8)	26.4 (15.7)	
$\Delta b^*$	4.5 (4.6)	5.3 (11.9)	0.398
absolute value ( $b^*$ )			
BA lesion	29.4 (7.2)	19.9 (18.4)	
surrounding BE	23.9 (8.1)	13.7 (10.2)	

WLI: white-light imaging, LCI: linked color imaging, BA: Barrett's adenocarcinoma, BE: Barrett's esophagus

ing larger than on WLI was attributed to the fact that many BA lesions had a red color, and  $a^*$ , which represents red color, was mainly increased by LCI.

In addition, we examined whether or not the color difference was increased on LCI depending on the morphology,

lesion color, and circumferential location of the lesion. Regarding the morphology, the color difference was increased by LCI for both protruding and flat to depressed lesions. LCI was considered useful for surveillance because the color difference was larger on LCI than with other imaging modalities, regardless of the form. BA has been reported to include many reddish lesions (30). In the present study, 85.7% of the subjects showed redness, and LCI may be useful for red lesions. In addition to reddish lesions, LCI also maximized the color difference in discolored lesions. Regarding the circumferential location of the lesion, most BA lesions are located in the 0-3 o'clock direction (30). Here as well, the color difference was increased on LCI, regardless of the circumferential location of the BA lesion. These results suggest that LCI may be useful regardless of the lesion morphology, color, and circumferential location.

Some lesions are very inconspicuous and difficult to find, particularly in LSBE. In the present study, there were four cases of LSBE. The slightly reddish 0-IIb lesion in LSBE and the discolored 0-IIc lesion in LSBE are both presented in Fig. 2 and 3, and in both of these cases, LCI showed a larger color difference than WLI or BLI (Fig. 2, 3). Regarding other two LSBE cases, LCI also showed a larger color difference than WLI or BLI. Therefore, LCI might be useful for the surveillance of BA in LSBE.

The diagnosis of superficial BA is complex. In Western

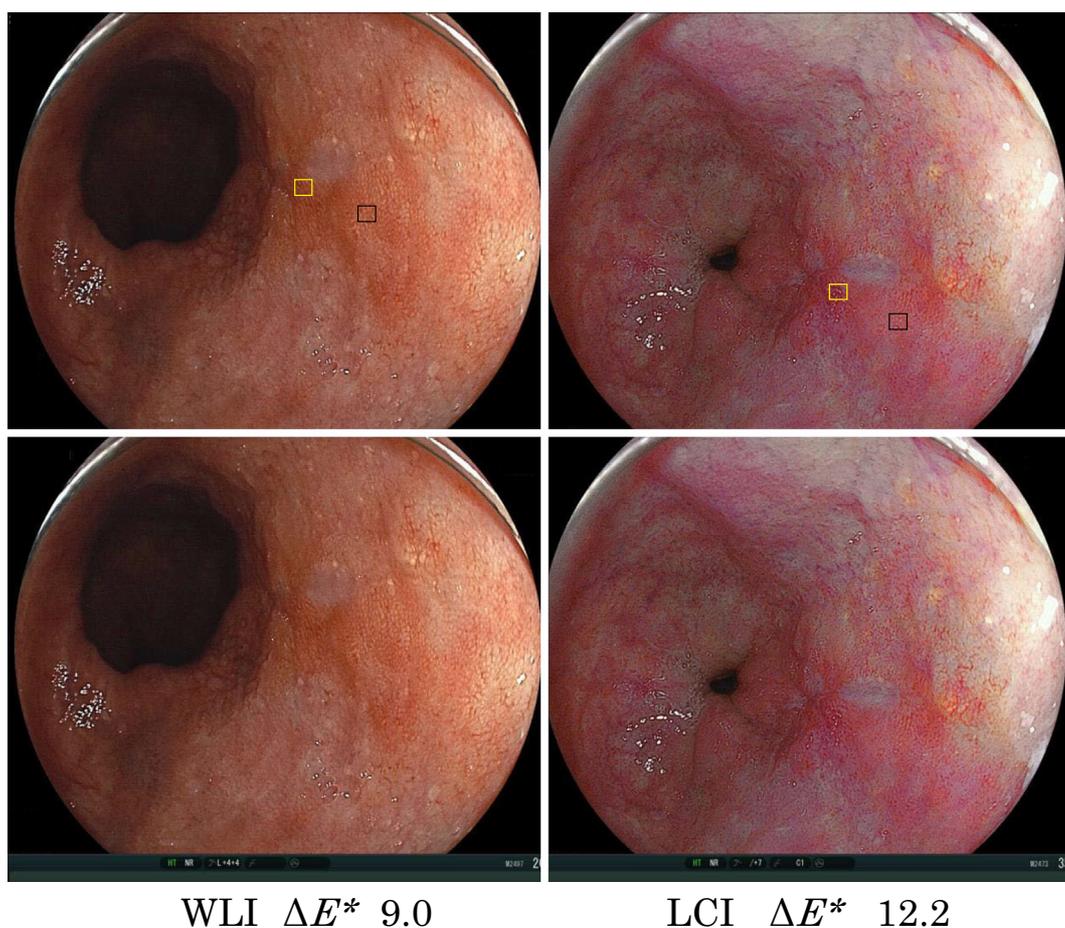
**Table 3. Observation Method with the Largest Color Difference.**

Color of the BA lesion	Reddish (n=18)	Discolored (n=3)
WLI	2	-
BLI	1	-
LCI	15	3

Circumference of the BA lesion	0-3 o'clock (n=17)	Other (n=4)
WLI	2	-
BLI	1	-
LCI	14	4

BA: Barrett's adenocarcinoma, WLI: white-light imaging, BLI: blue light imaging, LCI: linked color imaging

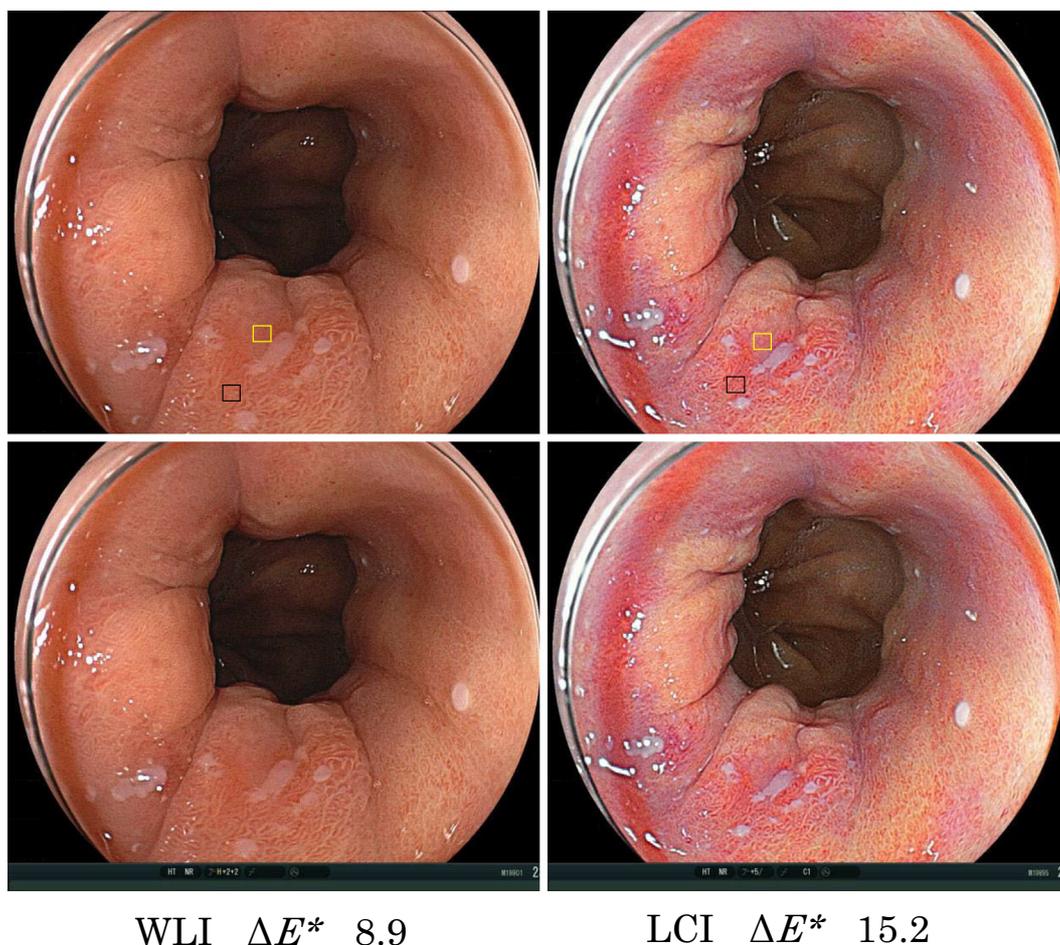


**Figure 2.** A comparison of the color difference in Case 1 that was difficult to detect by WLI within LSBE. The case was a slightly reddish 0-IIb lesion in the 3 o'clock direction in LSBE. The color difference on LCI was larger than that on WLI. The endoscopic pictures of WLI are on the left, and those of LCI are on the right. The upper pictures show the ROI: the yellow square indicates the ROI within the lesion, and the black squares indicate the ROI outside the lesion. The lower pictures were unmarked endoscopic images with the ROI.

countries, the Seattle Protocol with a random biopsy is recommended for the surveillance of BA (9). However, in Japan, a random biopsy is rarely performed in the surveillance of BA, and a detailed endoscopic examination with a targeted biopsy is usually considered the most common and efficient method for the early detection of BA (10-12, 30). As a targeted biopsy requires an accurate endoscopic diagnosis,

LCI can increase the color difference between a BA lesion and the surrounding mucosa and may thus support the diagnosis and screening of superficial BA.

Several limitations associated with the present study warrant mention. First, this study was a single-center retrospective study. Second, there were few BA lesions because the target lesions were limited to superficial cancers. Third, the



**Figure 3.** A comparison of the color difference in Case 2 that was difficult to detect by WLI within LSBE. The case was a discolored 0-IIc lesion in the 7 o'clock direction in LSBE. The color difference on LCI was larger than that on WLI. The endoscopic pictures of WLI are on the left, and those of LCI are on the right. The upper pictures show the ROI: the yellow square indicates the ROI within the lesion, and the black squares indicate the ROI outside the lesion. The lower pictures were unmarked endoscopic images with the ROI.

ROI was one point inside and outside the lesion due to the small lesion size and surrounding Barrett's mucosa being narrow in SSBE. However, this is the first study to verify LCI in the diagnosis of superficial BA based on the color difference. While LCI may be useful for the surveillance of superficial BA, further studies are required.

### Conclusion

LCI increases the color difference between BA and the surrounding Barrett's mucosa.

The study protocol was approved by the Institutional Ethics Committee of the Tohoku University School of Medicine, Sendai, Japan. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the 1964 Declaration of Helsinki and later versions. This is a retrospective study, and our obtaining informed consent via an opt-out method was approved by the ethics committee.

The authors state that they have no Conflict of Interest (COI).

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