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Characteristics of Superficial Gastric Neoplasms Detected Not by White Light Imaging but by Linked Color Imaging

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ABSTRACT

Background and Aims: Laser endoscopy has a linked color imaging (LCI) mode which has been reported to be superior to white light imaging (WLI) in detecting early gastric cancer (EGC). In this study, we retrospectively investigated the characteristics of superficial gastric neoplasms detected not by WLI but by LCI.

Patients and Methods: From April 2018 to May 2023, EGC or gastric adenoma identified by EGD was observed using LCI after WLI. The size, location, macroscopic type, color, skill level of the endoscopists, and treatment were examined for lesions detected by WLI (WLI group) and lesions detected not by WLI but by LCI (LCI group).

Results: Eighty-eight lesions of EGCs were differentiated adenocarcinomas, 13 undifferentiated adenocarcinomas, and 28 gastric adenomas. There were 117 lesions (90.7%) in the WLI group and 12 (9.2%) in the LCI group. The mean diameter was 22.9 mm in the WLI group and 9.3 mm in the LCI group, with the latter being significantly smaller ($p = 0.003$). The numbers of protruding, depressed, and flat lesions were 58, 59, and 0 in the WLI group, and 7, 4, and 1 in the LCI group, respectively, indicating that more protruding lesions were detected in the LCI group ($p = 0.005$). After multivariate analysis, there was a significant difference in diameter only in the LCI group compared to the WLI group (odds ratio, 0.834; 95% CI, 0.728–0.956).

Conclusions: LCI is more useful than WLI for detecting smaller superficial gastric neoplasms.

1 | Introduction

Gastric cancer (GC) is the fifth-most common cause of cancer-related mortality worldwide [1]. However, the 5-year survival rate of patients with early-stage GC (EGC) is > 90% [2, 3]. Most GCs are associated with chronic atrophic gastritis and intestinal metaplasia associated with *Helicobacter pylori* infection [4, 5]. Eradication of *H. pylori* infection may decrease the incidence of EGC [6–9]; however, it cannot entirely eliminate GCs. Therefore, surveillance using EGD after eradication of *H. pylori* infection is important for detecting EGC. However, it is sometimes difficult to detect EGC in the eradicated gastric mucosa [10]. Image-enhanced endoscopy is more useful than conventional white light imaging (WLI) for the detection and diagnosis of GC. Laser endoscopy (Fujifilm Medical Systems, Tokyo, Japan) has a blue laser imaging (BLI) mode and a linked color imaging (LCI) mode, which enhances reddish colors [11, 12]. LCI has been reported to improve the visibility and color contrast of EGC compared to WLI; however, this was determined retrospectively by comparing images obtained using LCI and WLI [11–21]. Ono et al. [22] reported that LCI is more effective than WLI in detecting

neoplastic lesions in the upper gastrointestinal tract. Min et al. [23] reported that LCI has better accuracy than WLI, both of which were employed in a prospective study. However, the characteristics of EGC detected by LCI have not been clarified in such studies.

This study retrospectively investigated the characteristics of superficial gastric neoplasms detected not by the WLI but LCI.

2 | Patients and Methods

Between April 2018 and May 2023, EGC or gastric adenoma first identified at our center by EGD using the Fuji Film System were investigated retrospectively. Patients aged > 20 years who underwent screening for EGD regardless of eradication of *H. pylori* infection or history of endoscopic submucosal dissection (ESD) for EGCs. Atrophic gastritis was endoscopically diagnosed according to the Kimura–Takemoto classification system [24]. Patients positive for *H. pylori* infection were defined as those positive for serum anti-Hp antibody, culture, or histopathologic findings from a gastric biopsy specimen, urea breath test, or fecal *H. pylori* antigen detection. Patients negative for *H. pylori* infection were defined as those negative for serum anti-Hp antibody, urea breath test, or fecal *H. pylori* antigen detection. Patients with upper gastrointestinal bleeding, those who had undergone gastrectomy, and those with advanced GC were excluded.

EGD was performed under local pharyngeal anesthesia without injection of scopolamine butylbromide or glucagon. Midazolam (1–5 mg) was administered for conscious sedation upon patient request. Each EGD was performed by one of seven endoscopists, three of whom were experts who had performed > 3000 EGDs, and the other four were trainees who had performed < 3000 EGDs. Each endoscopist performed at least 20 bright LCI and BLI examinations prior to the start of the study. The endoscopes used were EG-L580NW7, EG-L590WR, and EG-L600ZW7 with LASEREO 6000 or 7000 (Fujifilm Co. Tokyo, Japan).

In the WLI mode, observations from the antrum to the body in the retroflex during withdrawal, from the upper body to the lower body in the retroflex during insertion, and from the lower body to the upper body during withdrawal were conducted. Next, in the LCI mode, observation from the body to the antrum during insertion and from the lower body to the upper body in the retroflex position during withdrawal were conducted. When gastric neoplasms were suspected in the WLI and LCI modes, the mode was changed to BLI mode with or without magnification. Indigo carmine was sprayed when gastric neoplasms were suspected. Lesion sizes were measured endoscopically using open biopsy forceps or forceps. Finally, biopsy specimens were obtained for histopathologic diagnosis. Such endoscopic observation procedures were protocolized for the period of this study at our center. The WLI group included EGCs or gastric adenomas that were detected by the first WLI. The LCI group included EGCs or gastric adenomas that were detected not by the first WLI but by the next LCI. We compared background gastric mucosa, size, location, morphology, color, histopathology, and depth of invasion of gastric neoplasms. Each lesion was resected by ESD or surgery.

All the resected specimens were immediately fixed in 10% buffered formalin and stained with hematoxylin and eosin. Histopathologic evaluations were performed by several gastrointestinal pathologists blinded to the study protocol. Histology was evaluated according to the Paris classification.

TABLE 1 | Characteristics of gastric neoplasms.

Sex (male/female)	93/30
Mean age	76.0
H. pylori infection	
Positive	21 (17.1)
Negative	102 (82.9)
Background mucosa	
C-0, *n* (%)	2 (1.6)
C-1,2, *n* (%)	1 (0.8)
C-3, O-1, *n* (%)	11 (8.9)
O-2.3, *n* (%)	109 (88.6)
Gastric neoplasm	
Early gastric cancer, *n* (%)	101 (78.3)
Differentiated adenocarcinoma, *n* (%)	88 (68.2)
Undifferentiated adenocarcinoma, *n* (%)	13 (10.1)
Gastric adenoma, *n* (%)	28 (21.7)
Mean diameter (mm)	21.6 (5–70)
Location	
Upper portion, *n* (%)	21 (16.3)
Middle portion, *n* (%)	54 (41.9)
Lower portion, *n* (%)	54 (41.9)
Morphology	
Protruded type, *n* (%)	65 (50.4)
Depressed type, *n* (%)	63 (48.8)
Flat type, *n* (%)	1 (0.8)
Depth	
Mucosa, *n* (%)	97 (75.2)
Submucosa, *n* (%)	32 (24.8)
Treatment	
ESD, *n* (%)	100 (77.5)
Surgery, *n* (%)	29 (22.5)

Abbreviation: ESD, endoscopic submucosal dissection.

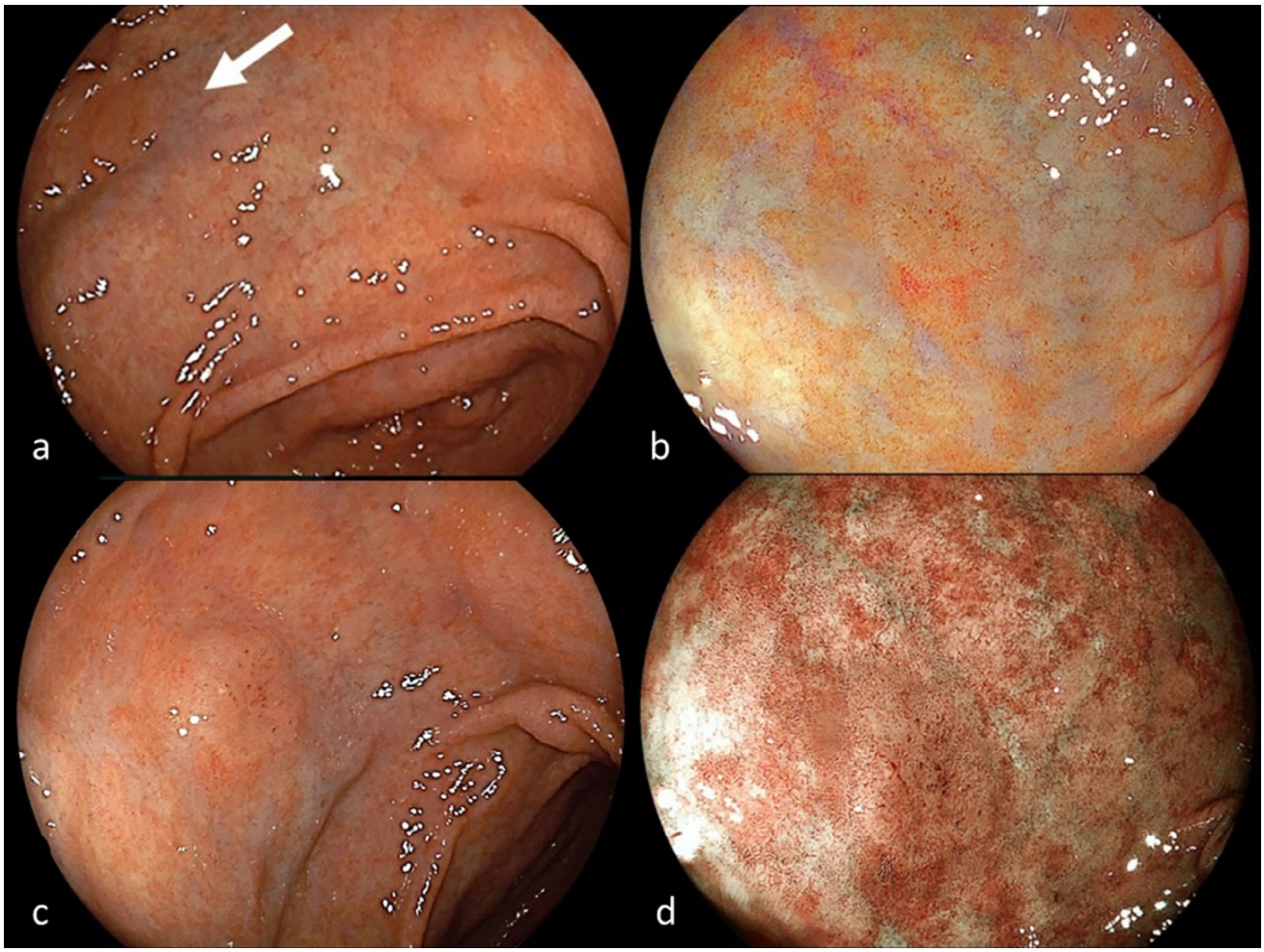

FIGURE 1 | Early-stage gastric cancer: Flat elevated lesion. (a): First white light imaging, the lesion is overlooked. (b): Linked color imaging, orange-red lesion. (c): Second white light imaging, slightly reddish lesion. (d): Blue laser imaging.

The study protocol was in accordance with the tenets of the revised Declaration of Helsinki (1989) and was approved by the institutional review boards of our institutions (2023-053).

3 | Statistical Analysis and Sample Size Calculation

Fisher's exact test was used to analyze categorical data and compare proportions, whereas Mann–Whitney *U*-test was used to analyze continuous data. Statistical significance was set at $p < 0.05$. We performed additional logistic regression analysis to assess the characteristic factors of gastric lesions in the LCI group compared with those in the WLI group. All statistical analyses were performed using IBM SPSS software v.24 (SPSS Inc. Chicago, IL, USA).

4 | Results

In total, 101 EGC lesions (78.3%) and 28 gastric adenomas (21.7%) in 123 patients were included. Ninety-three patients were male and 30 were female; the mean age was 76.0 years. Among *H. pylori*-negative patients, 84 (68.3%) underwent successful eradication therapy for *H. pylori* infection and another 18 patients (14.6%) did not undergo eradication therapy. Two patients (1.6%) had no atrophic gastritis (C-0), one (0.8%) had C-1, 2 atrophic gastritis, 11 (8.9%) had C-3 and O-1 atrophic gastritis, and 109 (88.6%) had O-2 and O-3 atrophic gastritis (Table 1). Among the EGCs, 88 (68.2%) were differentiated and 13 (10.1%) were undifferentiated. The mean gastric lesion diameter was 21.6 mm. Twenty-one (16.3%) lesions were located in the upper portion, 54 (41.9%) in the middle portion, and 54 (41.9%) in the lower portion. Sixty-five (50.4%) lesions protruded, 63 (48.8%) were depressed, and one (0.8%) was flat. The depth was the intramucosal layer in 97 lesions and the submucosal layer in 32 lesions (Table 1).

Ninety-two EGCs and 25 gastric adenomas (90.7%) were detected at the first WLI (WLI group), and nine EGCs and three gastric adenomas (9.3%) were overlooked by the first WLI; however, these were detected using LCI (LCI group) (Figures 1–3). All of these were detected after the second WLI.

The mean diameter of the lesions in the WLI group was 22.9 mm, while that in the LCI group was 9.3 mm, all lesions in the LCI group were < 15 mm in diameter. Lesions were significantly smaller in the LCI group than in the WLI group ($p = 0.003$)

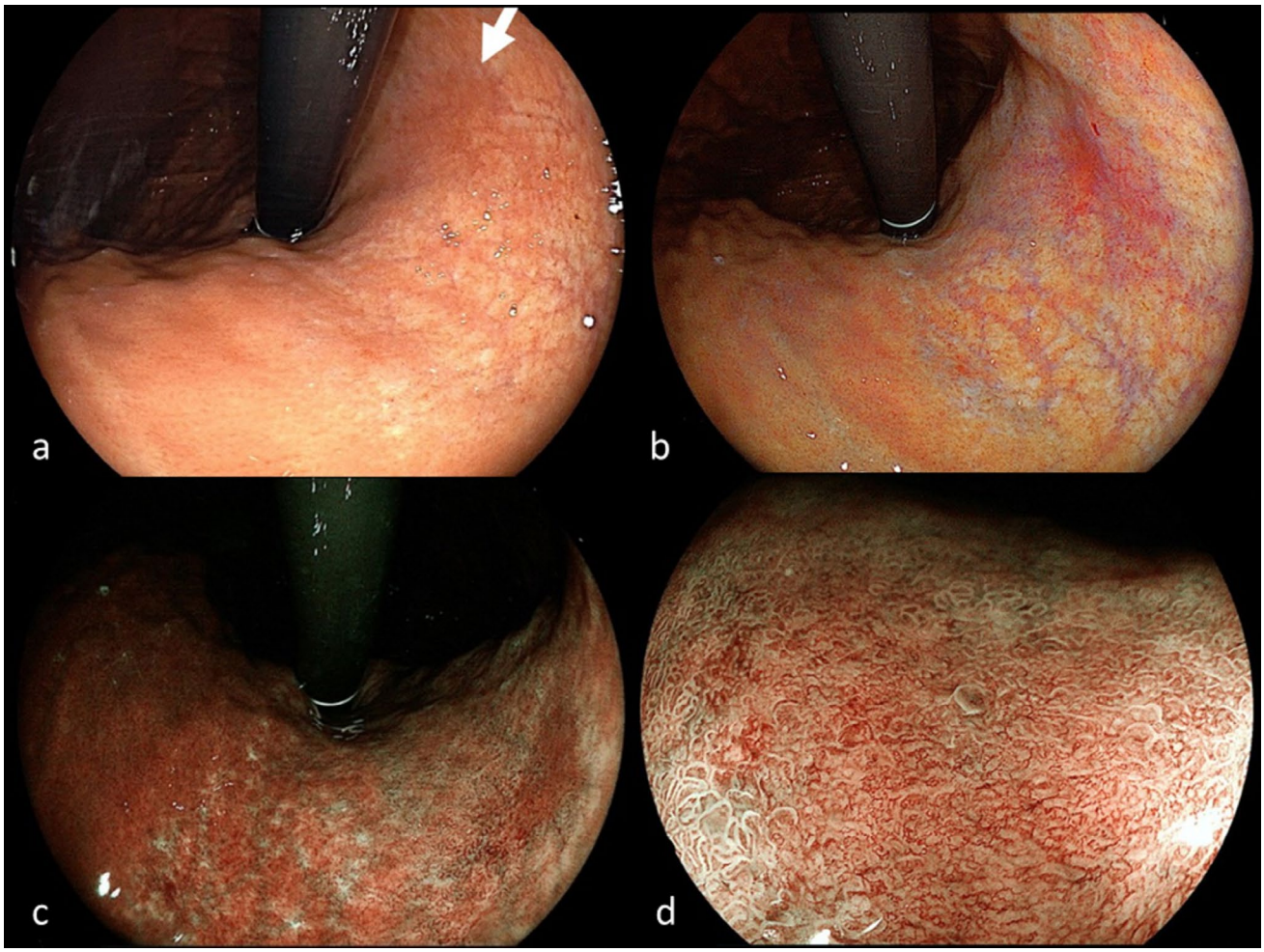

FIGURE 2 | Early-stage gastric cancer: Flat lesion. (a): White light imaging, the lesion is overlooked. (b): Linked color imaging, the orange-red lesion. (c): Blue laser imaging. (d): Magnified image with blue laser imaging.

(Table 2). There were no significant differences in the location, color, or depth between the WLI and LCI groups. The numbers of protruded and depressed lesion types in the LCI group were almost equal; however, the number of protruded types was higher than that of depressed types in the LCI, indicating a significant difference in the morphology between the WLI and LCI groups ($p = 0.005$). There were no significant differences in the numbers of endoscopists between the WLI and LCI groups (Table 2).

In multivariate analysis, there was a significant difference only in lesion diameter in the LCI group compared to that in the WLI group (odds ratio, 0.834; 95% confidence interval (CI), 0.728–0.956) (Table 3).

All lesions in the LCI group and 75% of lesions in the WLI group were resected endoscopically. Those in the LCI group tended to be resected endoscopically more often those in the WLI group ($p = 0.067$).

5 | Discussion

It has been reported that LCI improves the visibility of superficial gastric neoplasms compared to WLI [13–21]. However, these data were retrospectively analyzed using still endoscopic images. Ono et al. [22] reported that LCI is more effective than WLI for detecting neoplastic lesions in the upper gastrointestinal tract, including EGC, esophageal cancer, and pharyngeal cancer; however, there was no significant difference in the detection of only GC between LCI and WLI. Min et al. reported that the diagnostic accuracy for EGC is 78.8% using LCI and 68.4% using WLI ($p < 0.0001$), and that LCI shortened the examination time compared with WLI ($p = 0.019$) [23]. These studies did not show the characteristics of gastric lesions detected using LCI, such as size, location, morphology, color, and background mucosa. Kato et al. [25] reported that in a successful eradication group, more gastric lesions were detected in the primary mode in the LCI group than in the WLI group, indicating that more lesions were missed by WLI. Yamaoka et al. [26] reported that gastric lesions missed in WLI mode but detected in LCI mode were smaller than those detected in WLI mode; however, the sample size was too small.

In this study, 12 (9.3%) of 129 lesions were detected not by the WLI but by the LCI. In univariate analysis, lesions in the LCI group were smaller than those in the WLI group, and the rate of protruded-type lesions in the LCI group was higher than that in the WLI group. However, in multivariate analysis, there was a significant difference only in lesion diameter between the LCI

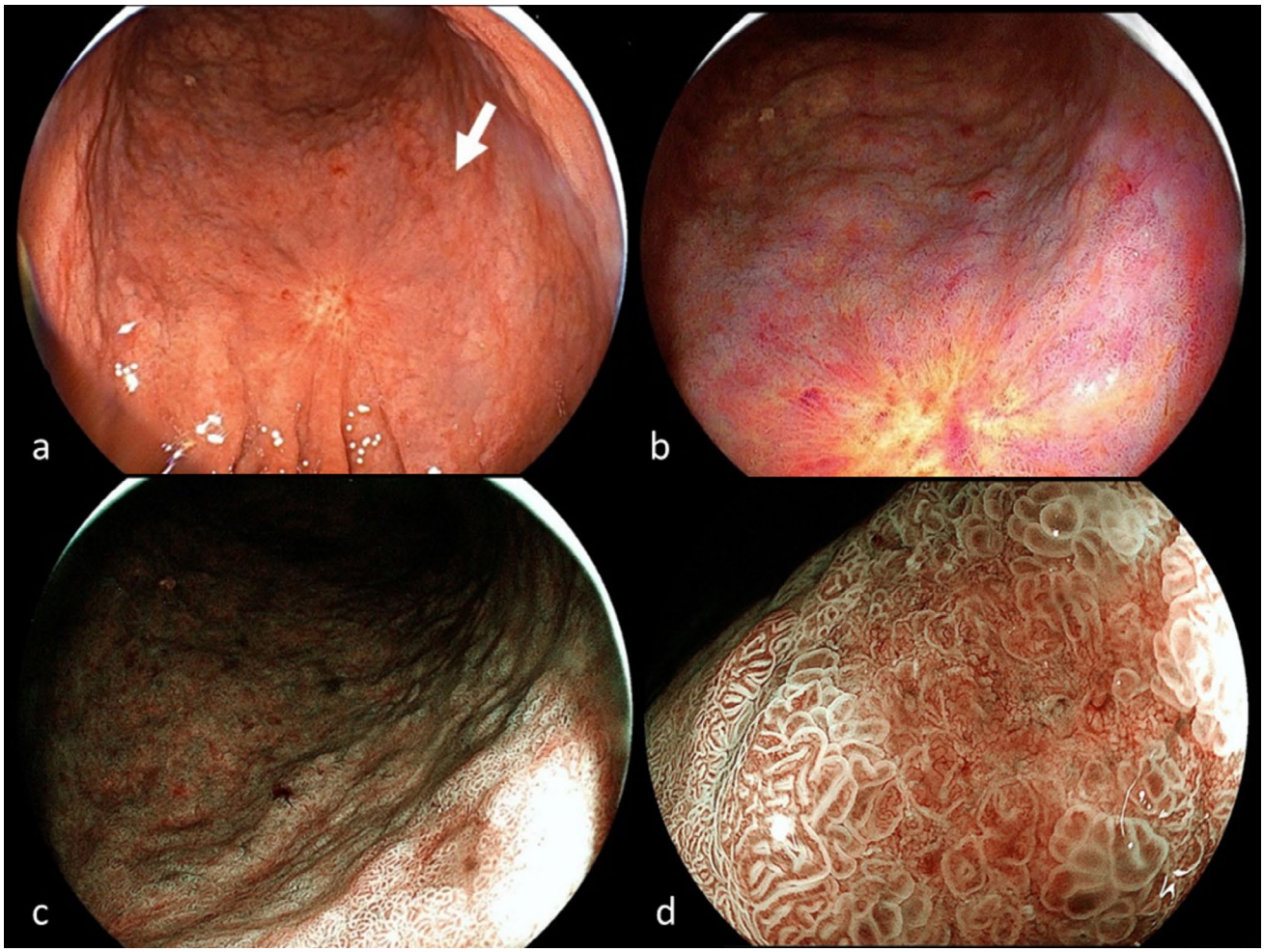

FIGURE 3 | Early-stage gastric cancer: Flat depressed lesion. (a): White light imaging, the lesion is overlooked. (b): Linked color imaging, orange-red lesion. (c): Blue laser imaging. (d): Magnified image with blue laser imaging.

and WLI groups. Because of the small sample size, there might be differences in the morphology in univariate analysis but not in multivariate analysis.

After the detection of lesions by the LCI, all lesions could be detected by the second WLI. Once lesions were detected by the LCI, they could then be detected by the WLI, even if the lesions were small. Because the LCI enables clearer color enhancement of lesions, it renders reddish lesions more reddish and white lesions; therefore, it enhances the color contrast of lesions against the surrounding atrophic gastric area [14, 18]. Khurelbaatar et al. [21] reported that the LCI has advantages such as better visibility of lesions of a size within the endoscopic treatment range, including those ≤ 10 mm: the same as larger lesions. However, it causes not only gastric neoplasms but also redness or erosion due to gastric inflammation being more visible [27]. Redness or erosion may be misdiagnosed only in the LCI if endoscopists do not have sufficient training for observations in the LCI. Focken reported that experts reached a higher consensus on the discrimination between neoplasia and inflammation when using the LCI, and nonexperts improved their targeted biopsy placement with the use of the LCI [28]. In this study, there were no significant differences in endoscopists between the two groups, indicating that some gastric lesions that were not detected by the WLI could be detected by the LCI by both trainees and trainers. It has been reported that the detection of GCs and diagnosis of GC margins becomes more difficult because the mucosa in chronic gastritis is changed, the height of tumors is decreased, and the tumor surface is covered with normal epithelium or low-grade atypia after the successful eradication of *H. pylori* infection [10]. In this manner, the superficial mucosa in GC becomes similar to that of the surrounding mucosa in chronic gastritis.

All lesions in the LCI group were endoscopically resected, on the other hand, 88 of 117 lesions in the WLI group were resected endoscopically and 29 lesions were resected surgically. The detection of smaller lesions in the LCI allows for ESD and might make treatment for those lesions less invasive.

This study had certain limitations. This was a retrospective, single-center study, and the sample size of patients with gastric neoplasms was small. Moreover, the study protocol had one arm of detection using LCI following WLI only, without a comparison arm of detection using WLI following LCI or the first WLI following the second WLI. If a second endoscopic observation is performed using the same WLI, there should be newly detected lesions. In the near future, a multicenter,

TABLE 2 | Characteristics of gastric neoplasms in WLI and LCI groups.

	WLI ($n=117$)	LCI ($n=12$)	p
H. pylori infection			0.434
Positive	20	1	
Negative	97	11	
Background mucosa			0.878
C-0, *n*	2	0	
C-1,2, *n*	0	0	
C-3, O-1, *n*	12	1	
O-2.3, *n*	103	11	
Mean diameter (mm)	22.9	9.3	0.001
Location			0.654
Upper portion	18	3	
Middle portion	49	5	
Lower portion	50	4	
Background mucosa			0.648
Atrophic area	115	12	
Nonatrophic area	2	0	
Color			0.307
Reddish	81	10	
Whitish	36	2	
Morphology			0.005
Protruded type	58	7	
Depressed type	59	4	
Flat type	0	1	
Depth			0.165
Mucosa	86	11	
Submucosa	31	1	
Endoscopist			0.862
Trainer	85	9	
Trainee	32	3	
Treatment			0.067
ESD	88	12	
Surgery	29	0	

Abbreviations: ESD, endoscopic submucosal dissection; LCI, linked color imaging; WLI, white light imaging.

prospective, randomized trial of gastric neoplasm characteristics between the WLI and LCI groups with a large sample size is needed.

TABLE 3 | Multivariate analysis of characteristic factors of gastric lesions in the LCI group compared with the WLI group.

	Odds ratio (95% CI)	p
Diameter	0.834 (0.728–0.956)	0.009
Morphology	0.905 (0.25–3.283)	0.88

Abbreviation: CI, confidential interval.

In conclusion, LCI is more useful than WLI for the detection of smaller superficial gastric neoplasms and might make treatment for those lesions less invasive.

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Consent

The study period was from April 2018 to May 2023. The study protocol was in accordance with the tenets of the revised Declaration of Helsinki (1989) and was approved by the Institutional Review Boards of our institutions (2023-053). Because this is a retrospective study, informed consent was not obtained from the patients; however, information about the study was made public and patients were guaranteed the opportunity to refuse.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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