ORIGINAL RESEARCH

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Linked Color Imaging Focused on Neoplasm Detection in the Upper Gastrointestinal Tract

A Randomized Trial

Shoko Ono, MD, PhD*; Kenro Kawada, MD, PhD*; Osamu Dohi, MD, PhD; Shinji Kitamura, MD, PhD; Tomoyuki Koike, MD, PhD; Shinichiro Hori, MD, PhD; Hiromitsu Kanzaki, MD, PhD; Takahisa Murao, MD, PhD; Nobuaki Yagi, MD, PhD; Fumisato Sasaki, MD, PhD; Keiichi Hashiguchi, MD, PhD; Shiro Oka, MD, PhD; Kazuhiro Katada, MD, PhD; Ryo Shimoda, MD, PhD; Kazuhiro Mizukami, MD, PhD; Mitsuhiko Suehiro, MD; Toshihisa Takeuchi, MD, PhD; Shinichi Katsuki, MD, PhD; Momoko Tsuda, MD, PhD; Yuji Naito, MD, PhD; Tatsuyuki Kawano, MD, PhD; Ken Haruma, MD, PhD; Hideki Ishikawa, MD, PhD; Keita Mori, PhD; and Mototsugu Kato, MD, PhD, for the LCI-FIND Trial Group†

Background: Linked color imaging (LCI) is a new image-enhanced endoscopy technique that allows users to recognize slight differences in mucosal color.

Objective: To compare the performance of LCI with white light imaging (WLI) in detecting neoplastic lesions in the upper gastrointestinal tract.

Design: A controlled, multicenter trial with randomization using minimization. (University Hospital Medical Information Network Clinical Trials Registry: UMIN000023863)

Setting: 16 university hospitals and 3 tertiary care hospitals in Japan.

Patients: 1502 patients with known previous or current cancer of the gastrointestinal tract and undergoing surveillance for gastrointestinal cancer.

Intervention: WLI followed by LCI examination (WLI group) or LCI followed by WLI examination (LCI group).

Measurements: Diagnosis of 1 or more neoplastic lesions in the pharynx, esophagus, or stomach in the first examination (primary outcome) and 1 or more neoplastic lesions overlooked in the first examination (secondary outcome).

Results: 752 patients were assigned to the WLI group and 750 to the LCI group. The percentage of patients with 1 or more neoplastic lesions diagnosed in the first examination was higher with LCI than with WLI (60 of 750 patients or 8.0% [95% CI, 6.2% to 10.2%] vs. 36 of 752 patients or 4.8% [CI, 3.4% to 6.6%]; risk ratio, 1.67 [CI, 1.12 to 2.50; $P = 0.011$]). The proportion with overlooked neoplasms was lower in the LCI group than in the WLI group (5 of 750 patients or 0.67% [CI, 0.2% to 1.6%] vs. 26 of 752 patients or 3.5% [CI, 2.3% to 5.0%]; risk ratio, 0.19 [CI, 0.07 to 0.50]).

Limitation: Endoscopists were not blinded.

Conclusion: LCI is more effective than WLI for detecting neoplastic lesions in the pharynx, esophagus, and stomach.

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* Drs. Ono and Kawada contributed equally to this work.
† For members of the LCI-FIND Trial Group, see the **Appendix** (available at Annals.org).

The primary goal of upper gastrointestinal (GI) endoscopic examination is to detect neoplastic lesions in the pharynx, esophagus, and stomach. However, early-stage lesions may frequently be overlooked by conventional white light endoscopy (1–3).

Since the recent launch of image-enhanced endoscopy, many studies have evaluated its efficacy in diagnosing upper GI neoplasms as well (4–7). Most have focused on the evaluation of histologic diagnosis, whereas few have focused on neoplasm detection.

Muto and colleagues (8) reported the superiority of narrow band imaging (NBI) over white light imaging (WLI) in detecting superficial cancer of the head and neck or esophagus in a randomized comparative study. Dohi and coworkers (9) reported the superiority of blue laser imaging-bright over WLI in detecting superficial cancer of the stomach in a randomized comparative study.

The LASEREO system (Fujifilm Corporation), a new linked color imaging (LCI) technology that uses a laser, has been developed. With LCI images captured by simultaneous irradiations with white light and short-wavelength narrow band light at an appropriate ratio, simultaneous expansion and shrinkage of colors can be achieved to intensify shades of both red and white, allowing users to easily recognize subtle differences in mucosal color (**Appendix Figure 1**, available at Annals.org). Some reports have described the efficacy of LCI in the histologic diagnosis of neoplastic lesions in the upper GI tract (10–20), but no large-scale clinical studies have evaluated its efficacy in neoplasm detection.

We conducted a large-scale, multicenter, randomized, back-to-back comparative study to evaluate the performance of LCI compared with WLI in detecting neoplastic lesions in the upper GI tract, including the pharynx, esophagus, and stomach.

METHODS

Study Design

This study was designed as an open-label, parallel (1:1), multicenter, randomized controlled trial. The study protocol (**Supplement**, available at Annals.org) was designed by the steering committee and approved by the research ethics committee of the participating clinical

centers (30 September 2016, Tokyo Medical and Dental University). The trial recruitment occurred from 1 November 2016 to 31 July 2018. No major changes to study procedures or outcomes were made after trial commencement. This study followed the CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement (21) and was registered on 30 September 2016 in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000023863). All eligible patients provided written informed consent to participate. An independent efficacy and safety committee monitored patients' safety, adverse events, and progress during the trial.

Patients

This study included patients aged 20 to 89 years with known previous or current cancer of the GI tract (pharynx, esophagus, stomach, and large intestine) (22), presumably constituting a high-risk population for upper GI tract tumors. Upper GI endoscopy was scheduled in 16 university hospitals and 3 tertiary care hospitals throughout Japan. In routine clinical practice in Japan, upper GI endoscopy is performed in patients with a history of GI cancer to screen for metachronous tumors. It is also performed to confirm the presence or absence of synchronous cancer during detailed preoperative assessment in patients who have cancer and are referred from other hospitals. A series of patients who visited the participating institutions to receive routine medical care for these purposes were asked to participate in this study at each institution. Patients were excluded if they could not undergo biopsy or endoscopy, if they could not express their own will because of dementia or consciousness disturbance, or if informed consent could not be obtained.

This study was approved by the institutional review boards of all participating institutions. It was clearly stated in the informed consent document that the participating patients were free to withdraw their consent at any time.

Randomization

Patients were enrolled and assigned to treatment groups in a 1:1 ratio via a website. A minimization method with a random component was used to balance the groups with respect to the following adjustment factors: study site, because of known differences among the institutions regarding the backgrounds of enrolled patients, treatment, efficacy evaluation, and safety evaluation; age (≥70 or <70 years), because neoplastic lesion occurrence increases with age; presence or absence of current cancer, because of known differences in detection rates among metachronous, synchronous, and double cancers; and surgical history of gastric or esophageal resection, because the area of carcinogenic potential varies according to the presence or absence of the stomach or esophagus. We used the computerized minimization allocation system independently developed by the Medical Research Support Group. The patients were blinded to group allocation, but the endoscopists were not.

Procedure

Endoscopists who had performed at least 20 endoscopic procedures using LCI participated in this study. Endoscopic systems used in this study included LASEREO 4450, the LASEREO 7000 System, and upper GI endoscopes (EG-L590WR, EG-L590ZW, EG-L600ZW, EG-L600WR7, and EG-L600ZW7, as well as transnasal endoscopes, such as EG-L580NW and EG-L580NW7), all manufactured by Fujifilm Corporation.

Regarding the examination procedures, each location was examined for the presence or absence of lesions, using WLI followed by LCI or LCI followed by WLI, according to randomization. The specific examination procedure in the WLI group was to 1) examine the pharynx using WLI and record the findings; 2) switch to LCI, examine the pharynx, and record the findings; 3) examine the esophagus using WLI and record the findings; 4) examine the stomach using WLI and record the findings; 5) switch to LCI, examine the stomach, and record the findings; 6) perform a biopsy of any suspected neoplastic lesions in the stomach detected in steps 4 and 5; 7) examine the duodenum (not part of this study); 8) during examination of the stomach, perform dye spraying, magnifying endoscopy, or additional biopsy as needed (not part of this study); 9) switch to LCI, examine the esophagus while pulling out the endoscope, and record the findings; 10) perform a biopsy of any suspected neoplastic lesions in the esophagus detected in steps 3 and 9; 11) during examination of the esophagus, perform dye spraying, magnifying endoscopy, or additional biopsy as needed (not part of this study); and 12) perform a biopsy of any suspected neoplastic lesions in the pharynx detected in steps 1 and 2. Examinations in the LCI group were performed by reversing the order of LCI and WLI. Biopsy specimens of all lesions detected were subjected to histopathologic diagnosis.

Neoplastic lesions were defined as high-grade dysplasia or carcinomas in the pharynx, intraepithelial neoplasia or carcinomas in the esophagus, and adenoma or carcinomas in the stomach. Squamous intraepithelial neoplasia is essentially equivalent to low-grade dysplasia as specified by the World Health Organization (23).

The number of detected lesions, neoplastic or nonneoplastic, and endoscopists' confidence about potential for malignancy (that is, high vs. low) were recorded for each procedure during examination of each location.

Study End Points

The primary end point was the diagnosis of 1 or more neoplastic lesions in the pharynx, esophagus, or stomach by the first imaging method in the tandem examination. A secondary end point was 1 or more neoplastic lesions overlooked by the first imaging method (that is, neoplastic lesions detected by the second examination but not by the first). Patients must have undergone a prior medical examination to ensure that cancerous lesions known before study participation were not counted as lesions detected by endoscopy. Other secondary end points included adverse events and procedure time. The time necessary for ex-

amination of the esophagus and stomach was based on the examination times from start to finish for each location captured in the image files. A clock attached to the endoscopy equipment with photographic recording allowed the imaging procedure time to be determined.

We also characterized all neoplastic lesions detected by the first imaging method with respect to location, size, morphologic characteristics, and endoscopists' level of confidence in potential for malignancy.

Statistical Analysis

We calculated the minimum sample size using a traditional 2-sample proportion test. The cancer detection rate in endoscopic screening for metachronous cancer is approximately 3% (24). Thus, we considered 3% to be the detection rate by WLI. Because no data are available comparing the cancer detection rates by LCI and WLI, those for pharyngeal or esophageal and gastric cancer by LCI were assumed to be 3 and 1.5 times higher, respectively, than those by WLI, based on the report by Muto and colleagues (8), which described the detection rate for pharyngeal or esophageal cancer by NBI as being triple that by WLI. When the ratio of the enrolled patients with pharyngeal or esophageal cancer to those with gastric cancer was assumed to be 1:2, the detection rates by WLI and LCI were assumed to be 3% and 6%, respectively. With a significance level of 0.05 (2-sided) and power of 80%, the sample size adequate to detect significant differences was planned to be 750 patients per group, or 1500 in total.

The primary analysis compared the percentage of patients diagnosed with a neoplastic lesion in the pharynx, esophagus, or stomach in the first examination using either WLI or LCI (that is, incidence of neoplastic lesion). The denominator is the number of patients in each group, and the numerator is the number of patients diagnosed with 1 or more neoplastic lesions. The risk ratio was obtained by division of the incidence in the 2 groups, and the 95% CI values were calculated. The adjusted odds ratios were calculated using age, history of cancer, and surgical history as explanatory variables in multivariate logistic regression analysis of the presence of a new malignant lesion at the patient level as the independent variable.

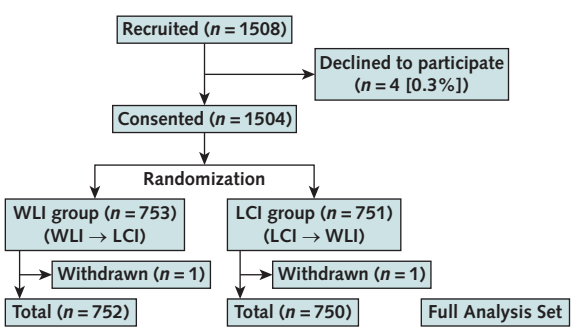
The secondary end point, 1 or more neoplastic lesions overlooked by the first imaging method (that is, neoplastic lesions detected by the second examination but not by the first) in each group, was analyzed similarly. Time of procedure was summarized with means (95% CIs). Lesion characteristics were summarized descriptively. Differences were considered significant if the *P* value was below 0.05 (2-tailed). Statistical analysis was performed using JMP, version 14.0 (SAS Institute), and R, version 3.6.0 (R Foundation).

Preliminary results were obtained at 6 months after initiation of the study by calculating the detection rate of neoplastic lesions in the 2 groups combined. These results were analyzed by the trial statistician. The detection rate of neoplastic lesions was assumed to be about 4.5% in the 2 groups as a whole. Had the actual rate been lower than the assumed rate, revision of the number of necessary cases was to be reconsidered in a meeting of the co-investigators. The preliminary results, without details, such as the number of endoscopic examinations in each group, were reported to each participating institution. No changes were made in the conduct of the study as a result of this preliminary analysis.

Role of the Funding Source

Fujifilm Corporation provided financial support and all medical equipment to the participating institutions, but an agreement was made between Fujifilm and the participating institutions that Fujifilm would not be involved in either design of the study or handling of the study results. Moreover, Fujifilm provided no support for writing or in any other way preparing the manuscript.

Figure. Trial profile.



Withdrawals: 1 unobservable case because of a high amount of gastric residue (WLI group) and 1 case of failed passage because of pharyngeal cancer (LCI group). LCI = linked color imaging; WLI = white light imaging.

RESULTS

Among 1508 patients invited to participate in this study between November 2016 and July 2018, 1504 were enrolled after giving consent: 753 were assigned to the WLI group and 751 to the LCI group. Two patients, one in each group, were excluded because of a large amount of residue (WLI group) and stenosis caused by pharyngeal neoplasm (LCI group). In all 752 patients in the WLI group and 750 patients in the LCI group were included in the analyses (**Figure**). Patient recruitment was discontinued when the target number of patients had been accrued. Demographic variables, including age (39.8% of patients <70 years in both groups), sex (76.8% in the WLI group and 77.6% in the LCI group were men), presence of surgical history (12.4% and 12.2%, respectively), current cancer (15.8% and 16.1%, respectively), and history of radiation therapy (11.7% in both groups), were similar in the 2 groups (**Table 1**; **Appendix Tables 1** and **2**, available at Annals.org).

Of the 58 endoscopists who performed endoscopies in this study, 23 detected tumors. The endoscopists performed a median of 15 (range, 1 to 231) endoscopies. Three endoscopists detected tumors in 15 or more patients. Nearly all of the endoscopists per-

formed endoscopies for patients in both groups. No particular trends were observed in the frequencies of lesion detection among the endoscopists (**Appendix Table 3**, available at Annals.org).

Representative LCI and WLI images of esophageal and gastric cancer are shown in **Appendix Figure 2** (available at Annals.org). The percentage of patients diagnosed with a neoplastic lesion in the first examination by LCI (60 [66 lesions] of 750 patients or 8.0% [95% CI, 6.2% to 10.2%]) was higher than that by WLI (36 [37 lesions] of 752 patients or 4.8% [CI, 3.4% to 6.6%]) with a relative detection ratio of 1.67 (CI, 1.12 to 2.50; P = 0.011). The combined number of patients diagnosed with neoplastic lesions in the first and second examinations was 65 (71 lesions) in the LCI group and 60 (63 lesions) in the WLI group, with no difference between groups (**Table 2**).

The proportion of patients with 1 or more overlooked neoplasms after LCI examination (5 of 750 patients or 0.7% [CI, 0.2% to 1.6%]) was lower than that by WLI (26 to 752 patients or 3.5% [CI, 2.3% to 5.0%]), with a risk ratio of 0.19 (CI, 0.07 to 0.50; $P < 0.001$). The results of the multivariable logistic regression for the primary end point and overlooked lesions were similar to the unadjusted risk ratios (**Table 2**).

The characteristics of the lesions detected in the first examination of the respective comparison groups are shown in **Table 3**. Pharyngeal neoplasms accounted for 5.4% of the lesions detected in the first examination in the WLI group and 10.6% in the LCI group. The corresponding proportions for the respective comparison groups were 27.0% and 27.3% for the esophagus and 67.6% and 62.1% for the stomach. The proportion of lesions strongly suspected of being malignant was 54.1% in the WLI group and 86.4% in the LCI group (**Table 3**). Among the detected neoplastic lesions, all cases of pharyngeal cancer were squamous cell carcinoma. All esophageal cancer cases were squamous cell carcinoma in the WLI group, whereas 2 (11.1%) lesions were intraepithelial neoplasia in the LCI group. As for gastric lesions, 3 (12.0%) adenoma cases were in the WLI group and also 3 (7.3%) in the LCI group. Gastric cancer detected included 1 diffuse type lesion (1 of 22; 4.6%) in the WLI group and 3 diffuse type lesions (3 of 38; 7.9%) in the LCI group; other gastric cancer lesions were of the intestinal type.

Appendix Table 4 (available at Annals.org) shows the proportion of detected tumors in all lesions biopsied. The proportion in the esophagus found to be neoplastic lesions was similar in both groups. The rates for pharyngeal and gastric lesions were slightly higher in the LCI group.

Table 4 provides the means and 95% CIs of the procedure times required for observation of the esophagus and stomach in the WLI and LCI groups in relation to the presence or absence of lesions. The distributions of the times necessary for observation of the esophagus were similar in the 2 groups. The procedure times for observation of the stomach were longer with LCI than WLI (mean difference, 16 seconds) except for the procedure time with lesions in the primary method. (These were not planned analyses.) No differences in the procedure times of the first or second endoscopic examinations of the esophagus were observed between the 2 groups. However, among patients without lesions, the mean values of the procedure times in the first and second examinations of the stomach with

Table 1. Baseline Characteristics of Study Participants*

Characteristic	WLI Group	LCI Group
Patients	753	751
Median age (IQR), *y*	71 (28–89)	72 (40–89)
Age <70 y	300 (39.8)	299 (39.8)
Male	578 (76.8)	583 (77.6)
Surgical history	93 (12.4)	92 (12.2)
Current cancer	119 (15.8)	121 (16.1)
History of radiation therapy	88 (11.7)	88 (11.7)

IQR = interquartile range; LCI = linked color imaging; WLI = white light imaging.
* Values reported are numbers (percentages), unless otherwise indicated.

Table 2. Patient-Based Results (Primary Results): Neoplastic Lesions Detected Using WLI and LCI in the Primary and Secondary Modes

Variable	WLI Group (n = 752)	LCI Group (n = 750)	Risk Ratio (95% CI)	*P* Value*	Adjusted Odds Ratio (95% CI)†
Total					
Patients, *n (% [95% CI])*	60 (8.0 [6.1–10.2])	65 (8.7 [6.8–10.9])	–	–	–
Lesions, *n*	63	71	1.09 (0.78–1.52)	0.63	1.09 (0.76–1.58)
Detected by primary mode (primary end point)					
Patients, *n (% [95% CI])*	36 (4.8 [3.4–6.6])	60 (8.0 [6.2–10.2])	–	–	–
Lesions, *n*	37	66	1.67 (1.12–2.50)	0.011	1.74 (1.13–2.66)
Detected by secondary mode‡					
Patients, *n (% [95% CI])*	26 (3.5 [2.3–5.0])	5 (0.7 [0.2–1.6])	–	–	–
Lesions, *n*	26	5	0.19 (0.07–0.50)	<0.001	0.19 (0.07–0.49)

LCI = linked color imaging; WLI = white light imaging.
* Applies to risk ratios.
† Obtained from a logistic regression analysis, adjusted for age, presence or absence of cancer, and surgical history.
‡ Only the lesions that were not detected by the first examination were counted among the number of lesions detected by the second examination.

LCI were 11.0 seconds (primary method) and 13.5 seconds (secondary method) longer than those with WLI (Table 4).

No serious adverse events were observed in either group.

DISCUSSION

This randomized clinical study demonstrated that LCI can detect neoplastic lesions in the upper GI tract (pharynx, esophagus, and stomach) 1.67 times (CI, 1.12 to 2.50) more frequently than WLI.

The detection rate for superficial pharyngeal or esophageal cancer is reportedly significantly higher with NBI than WLI (8). However, to our knowledge, no previous reports have described the detection of neoplastic lesions in the stomach by NBI. In the present study, the capability of LCI to identify gastric cancer tended to be higher than that of WLI at all locations examined, including the pharynx, esophagus, and stomach. Linked color imaging improves neoplasm detection, regardless of the location, because it allows for observation from a distance even in the stomach owing to its noninferiority to conventional WLI in terms of image brightness. It also can provide images resembling those obtained by conventional WLI as well as enhanced color contrast between areas of redness and discoloration (25, 26).

Various types of gastritis associated with *Helicobacter pylori* infection can progress to gastric cancer. Thus, differentiation between gastritis and gastric cancer is important for gastric cancer screening. Linked color imaging is reportedly effective in diagnosing active gastritis and gastric atrophy and detecting intestinal metaplasia, which may be difficult to identify using WLI (12, 13, 19). These observations indicate that LCI can detect gastric cancer more often than WLI in patients with various types of gastritis. Clinical and observational studies have reported the efficacy of LCI in detecting gastric cancer, but no randomized study has yet been reported (14–16, 20).

Randomized studies comparing WLI and LCI colonoscopy for detection of neoplastic lesions have been reported (27–29). A crossover randomized study showed that, of 2 colonoscopic examinations with WLI and LCI, the latter increased the overall detection rate of colorectal polyps and adenomas (30). A tandem

Table 3. Lesion-Based Results (Descriptive Results): Clinicopathologic Features of Lesions Detected in the WLI and LCI Groups and Endoscopic Confidence Prediction Using WLI and LCI (Only the First Procedure in Each Group)*

Variable (36 Patients/ 37 Lesions)	Detected by WLI in WLI Group	Detected by LCI in LCI Group (60 Patients/ 66 Lesions)
Site		
Pharynx		
Lesions	2 (5.4†)	7 (10.6‡)
SCC	2	7
Esophagus		
Lesions	10 (27.0†)	18 (27.3‡)
SCC	10	16
IN	0	2
Stomach		
Lesions	25 (67.6†)	41 (62.1‡)
Adenocarcinoma	22	38
Intestinal type	21	35
Diffuse type	1	3
Adenoma	3	3
Size		
≤10 mm	24 (64.9†)	39 (59.1‡)
>10 to 19 mm	9 (24.3†)	15 (22.7‡)
>19 mm	4 (10.8†)	11 (16.7‡)
Median, *mm*	12 (1–80)	11 (2–60)
Morphology		
Unidentified or untreated	0 (0†)	1 (1.5‡)
Mass	12 (32.4†)	15 (22.7‡)
Diffuse infiltrative	9 (24.3†)	11 (16.7‡)
Depressed	16 (43.2†)	40 (60.6‡)
Endoscopists' confidence about the neoplastic potential		
High	20	57
Low	17	9
Strongly suspected to be neoplastic, %	54.1†	86.4‡

IN = intraepithelial neoplasia; LCI = linked color imaging; SCC = squamous cell carcinoma; WLI = white light imaging.
* Values presented are the number (percentage) of lesions, unless otherwise indicated.
† (lesions detected by WLI in WLI group in each category)/(lesions detected by WLI in WLI group) * 100.
‡ (Lesions detected by LCI in LCI group in each category)/(lesions detected by LCI in LCI group) * 100.

Table 4. Procedure Times for the WLI and LCI Groups*

Variable	WLI Group	LCI Group
	WLI View (*n* = 752)	**LCI View (*n* = 750)**
Primary mode, *s*		
No lesion		
Esophagus	(*n* = 595) 65 (62–68)	(*n* = 582) 63 (61–66)
Stomach	(*n* = 586) 155 (148–162)	(*n* = 568) 166 (159–173)
With lesions		
Esophagus	(*n* = 157) 73 (66–80)	(*n* = 168) 74 (68–80)
Stomach	(*n* = 157) 170 (157–184)	(*n* = 167) 186 (172–200)
	LCI View (*n* = 752)	**WLI View (*n* = 750)**
Secondary mode, *s*		
No lesion		
Esophagus	(*n* = 595) 38 (36–40)	(*n* = 582) 38 (36–41)
Stomach	(*n* = 586) 115 (110–120)	(*n* = 568) 102 (98–105)
With lesions		
Esophagus	(*n* = 157) 45 (41–49)	(*n* = 168) 45 (40–50)
Stomach	(*n* = 157) 125 (117–132)	(*n* = 167) 114 (106–122)

LCI = linked color imaging; WLI = white light imaging.
* Values are presented as means (95% CIs).

colonoscopy study found that LCI decreased the rate of overlooking neoplastic lesions in the right colon and increased the detection rate for sessile serrated adenomas or polyps (27, 28). Taken together, the results of these studies and our present investigation indicate that LCI is effective for detecting neoplastic lesions throughout the GI tract, including the large intestine. Our study showed the usefulness of LCI in the upper GI tract, but whether upper GI cancer develops via the same mechanism as in the large intestine is unclear.

Techniques using LCI and WLI are immediately applicable to clinical practice utilizing the Fujifilm system because these imaging modes can easily be switched to the other during examination and are not as time-consuming and costly as dye spraying.

Equipment for LCI can easily be introduced because of its widespread global use, although a novel Fujifilm system, such as LASEREO in Japan or ELUXEO in the United States and Europe, needs to be purchased. Linked color imaging can be performed using these systems and already available endoscopes, such as a small-diameter endoscope for transnasal endoscopy and magnifying endoscopy, allowing detailed examination. The introduction of LCI from the beginning is more advantageous than using WLI alone. The longer procedure time for LCI may have been attributable to the fact that endoscopists were not very experienced in using LCI because it was a new technology, and LCI provides brighter images and higher visibility of entire images, thereby broadening the observation range. Because the increase in examination time is small, there is hardly an increase in the burden on patients. Potential overdiagnosis because of excessive detection of insignificant lesions may also be present; however, detected neoplastic lesions are amenable to endoscopic resection. Therefore, even if a lesion detected by LCI represents overdiagnosis, it may cause only minimal detrimental effects to a patient.

This study has limitations. The endoscopists were not blinded to the group allocation in this open-label study. The experts in upper GI endoscopy performed the examinations on populations at high risk for neoplasms in the pharynx, esophagus, or stomach. Thus, it is unclear whether these examinations, if performed by general clinicians on an average population, would yield results similar to those obtained by the highly experienced endoscopists in this study. However, LCI images resemble those obtained by conventional WLI. Thus, LCI can be expected to provide efficacy similar to that of conventional white light endoscopy even if general clinicians were to use LCI for cancer screening in an average population. The data for individual lesions were not analyzed in consideration of the correlation between the lesions (intra-individual correlations with patient factors), such that interpretation of lesion frequency requires further study. Lesion frequency must be interpreted carefully because we were not able to examine correlations between lesion and patient factors.

In the future, we aim to confirm the observed efficacy in studies using LCI, performed by general clinicians, in an average population.

The detection rate of neoplastic lesions in the upper GI tract by LCI was 1.67 times higher than that by WLI. This result indicates that many neoplastic lesions are being overlooked by conventional white light endoscopy performed in routine clinical practice. To reduce the rate of overlooking neoplasms, LCI should ideally be applied in clinical practice.

A large-scale randomized comparative study demonstrated LCI to be very effective in detecting neoplastic lesions in the pharynx, esophagus, and stomach when conducted for high-risk patients by experienced endoscopists, indicating that LCI should be recommended in screening for upper GI tract cancer. Further investigation is needed to determine whether this technique is similarly effective for the general population.

From Hokkaido University Hospital, Sapporo, Japan (S.O., M.T.); Tokyo Medical and Dental University, Tokyo, Japan (K.K.); Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan (O.D., Y.N.); Tokushima University Graduate School of Biomedical Sciences, Tokushima, Japan (S.K.); Tohoku University Graduate School of Medicine, Sendai, Japan (T.K.); National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan (S.H.); Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan (H.K.); Kawasaki Medical School, Okayama, Japan (T.M.); Asahi University Hospital, Gifu, Japan (N.Y.); Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan (F.S.); Nagasaki University Hospital, Nagasaki, Japan (K.H.); Hiroshima University Hospital, Hiroshima, Japan (S.O.); North Medical Center, Kyoto Prefectural University of Medicine, Kyoto, Japan (K.K.); Saga University, Saga, Japan (R.S.); Oita University, Oita, Japan (K.M.); Kawasaki Medical School General Medical Center, Okayama, Japan (M.S., K.H.); Osaka Medical College, Osaka, Japan (T.T.); Otaru Ekisaikai Hospital, Otaru, Japan (S.K.); Soka Municipal Hospital, Soka, Japan (T.K.); Kyoto Prefectural University of Medicine, Osaka, Japan (H.I.); Shizuoka Cancer Center, Shizuoka, Japan (K.M.); and National Hospital Organization Hakodate National Hospital, Hakodate, Japan (M.K.).

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Corresponding Author: Mototsugu Kato, MD, PhD, Department of Gastroenterology, National Hospital Organization Hakodate National Hospital, 18-16, Kawahara-chou, Hakodate, Hokkaido 041-8512, Japan; e-mail, mkato1957@gmail.com.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Drs. Ono and Tsuda: Division of Endoscopy, Hokkaido University Hospital, Nishi-5, Kita-14, Kita-ku, Sapporo, Hokkaido 060-8648, Japan.
Dr. Kawada: Department of Gastrointestinal Surgery, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.
Drs. Dohi and Naito: Department of Molecular Gastroenterology and Hepatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan.
Dr. Kitamura: Department of Gastroenterology and Oncology, Tokushima University Graduate School of Biomedical Sciences, 3-18-15, Kuramoto-cho, Tokushima 770-8503, Japan.
Dr. Koike: Division of Gastroenterology, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan.
Dr. Hori: Department of Endoscopy, National Hospital Organization Shikoku Cancer Center, 160 Kou Minamiumemoto-Machi, Matsuyama, Ehime 791-0280, Japan.
Dr. Kanzaki: Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan.
Dr. Murao: Division of Gastroenterology Department of Internal Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan.
Dr. Yagi: Department of Gastroenterology, Asahi University Hospital, 3-23, Hashimoto-chou, Gifu 500-8523, Japan.
Dr. Sasaki: Digestive and Lifestyle Diseases, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1, Sakuragaoka, Kagoshima 890-8520, Japan.
Dr. Hashiguchi: Department of Endoscopy, Nagasaki University Hospital, 1-7-1, Sakamoto, Nagasaki 852-8501, Japan.
Dr. Oka: Department of Endoscopy, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan.
Dr. Katada: Department of Gastroenterology and Hepatology, North Medical Center, Kyoto Prefectural University of Medicine, 481 Otokoyama Aza Yosanocho, Yosagun, Kyoto 629-2261, Japan.
Dr. Shimoda: Internal Medicine and Gastrointestinal Endoscopy, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan.
Dr. Mizukami: Department of Gastroenterology, Oita University, 1-1, Idaigaoka, Hasama, Yufu, Oita 879-5593, Japan.
Drs. Suehiro and Haruma: Department of General Internal Medicine 2, Kawasaki Medical School General Medical Center, 2-6-1, Nakasange, Kita-ku, Okayama 700-8505, Japan.
Dr. Takeuchi: Second Department of Internal Medicine, Osaka Medical College, 2-7, Daigaku-machi, Takatsuki, Osaka 569-8686, Japan.
Dr. Katsuki: Gastroenterology, Otaru Ekisaikai Hospital, 1-4-1 Inaho, Otaru, Hokkaido 047-0003, Japan.
Dr. Kawano: Department of Surgery, Soka Municipal Hospital, 2-21-1 Soka, Soka-shi, Saitama 340-8560, Japan.
Dr. Ishikawa: Department of Molecular-Targeting Cancer Prevention, Kyoto Prefectural University of Medicine, 3-2-17, Imabashi, Chuo-ku, Osaka 541-0042, Japan.
Dr. Mori: Clinical Research Promotion Unit, Clinical Research Center, Shizuoka Cancer Center, 1007, Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411- 8777, Japan.
Dr. Kato: Department of Gastroenterology, National Hospital organization Hakodate National Hospital, 18-16, Kawahara-chou, Hakodate, Hokkaido 041-8512, Japan.

Author Contributions: Conception and design: S. Hori, Y. Naito, T. Kawano, K. Haruma, M. Kato.
Analysis and interpretation of the data: T. Kawano.
Drafting of the article: S. Ono, K. Kawada, S. Hori, Y. Naito, M. Kato.
Final approval of the article: S. Ono, K. Kawada, O. Dohi, S. Kitamura, T. Koike, S. Hori, H. Kanzaki, T. Murao, N. Yagi, F. Sasaki, K. Hashiguchi, S. Oka, K. Katada, R. Shimoda, K. Mizukami, M. Suehiro, T. Takeuchi, S. Katsuki, M. Tsuda, Y. Naito, T. Kawano, K. Haruma, H. Ishikawa, K. Mori, M. Kato.
Provision of study materials or patients: S. Hori, T. Murao, R. Shimoda, K. Mizukami, M. Suehiro, S. Katsuki.
Statistical expertise: H. Ishikawa.
Obtaining of funding: R. Shimoda, M. Kato.
Administrative, technical, or logistic support: K. Haruma.
Collection and assembly of data: S. Ono, K. Kawada, O. Dohi, S. Kitamura, T. Koike, S. Hori, H. Kanzaki, N. Yagi, F. Sasaki, K. Hashiguchi, S. Oka, K. Katada, T. Takeuchi, S. Katsuki, M. Tsuda, Y. Naito, T. Kawano.

Appendix: Members of the LCI-FIND Trial Group

Hokkaido University Hospital: Yuichi Shimizu, MD, PhD†; Satoshi Abiko, MD, PhD†; Keiko Yamamoto, MD, PhD†; Takahiko Kudo, MD, PhD†; Kana Matsuda, MD, PhD†

Graduate School of Medical Science, Kyoto Prefectural University of Medicine: Kazuhiro Kamada, MD, PhD†; Takahiro Nakano, MD†; Kei Terasaki, MD†; Shun Takayama, MD†; Kazuyuki Ogita, MD†

Tokyo Medical and Dental University: Yasuaki Nakajima, MD, PhD†

Tokushima University, Graduate School of Biomedical Sciences: Tetsuji Takayama, MD, PhD†; Hironori Wada, MD†; Masanori Takehara, MD†; Kaizou Kagemoto, MD, PhD†; Fumika Nakamura, MD†

Tohoku University Graduate School of Medicine: Atsushi Masamune, MD, PhD†; Waku Hatta, MD, PhD†

Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences: Hiroyuki Okada, MD, PhD†; Masaya Iwamuro, MD, PhD†; Makoto Abe, MD, PhD†; Tatsuhiro Gotoda, MD, PhD†; Hiroyuki Sakae, MD, PhD†

Kawasaki Medical School: Akiko Shiotani, MD, PhD†; Hiroshi Matsumoto, MD, PhD†; Minoru Fujita, MD, PhD†; Motoyasu Oosawa, MD†

Asahi University Hospital: Tatsushi Omatsu, MD, PhD†; Takeshi Yasuda, MD†

Kagoshima University Graduate School of Medical and Dental Sciences: Akio Ido, MD, PhD†; Hidehito Maeda, MD†; Masayuki Kabayama, MD†

Nagasaki University Hospital: Ken Ohnita, MD, PhD†; Kazuhiko Nakao, MD, PhD†

Hiroshima University Hospital: Shinji Tanaka, MD, PhD†; Takahiro Kotachi, MD, PhD†

North Medical Center, Kyoto Prefectural University of Medicine: Akifumi Fukui, MD, PhD†; Akito Harusato, MD, PhD†; Kouhei Oka, MD†

Saga University: Takashi Akutagawa, MD, PhD†

Oita University: Kazunari Murakami, MD, PhD†; Ryo Ogawa, MD†

Kawasaki Medical School General Medical Center: Hirofumi Kawamoto, MD, PhD†; Ken Haruma, MD, PhD*

Osaka Medical College: Kazuhide Higuchi, MD, PhD†; Yuichi Kojima, MD, PhD†; Kazuhiro Ota, MD, PhD†

National Hospital Organization, Hakodate National Hospital: Katsuhiro Mabe, MD, PhD†; Kimitoshi Kubo, MD, PhD†

* Author.

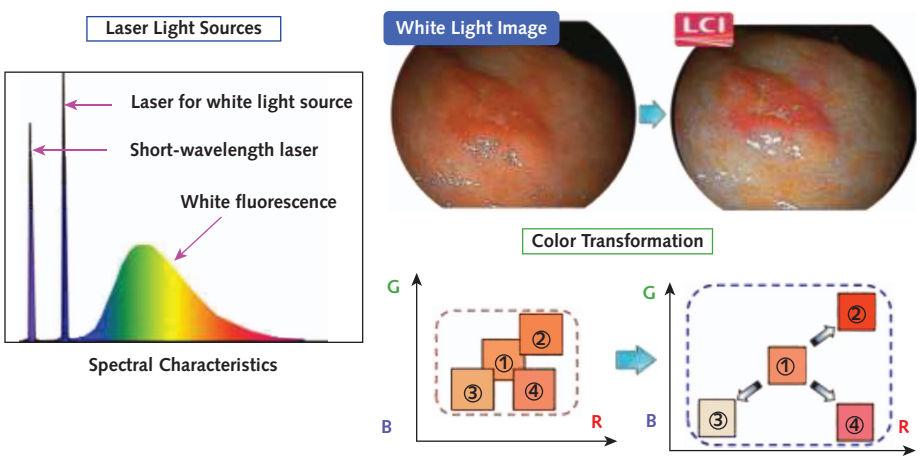
† Nonauthor contributor.

Appendix Table 1. Patients With Current Cancer, by Site

Site	WLI Group, *n*	LCI Group, *n*	Total, *n*
Head and neck	21	22	43
Esophagus	16	23	39
Stomach	62	64	126
Duodenum	–	1	1
Large intestine	15	9	24
Head and neck/esophagus	2	–	2
Esophagus/stomach	2	2	4
Stomach/large intestine	1	–	1
Total	119	121	240

LCI = linked color imaging; WLI = white light imaging.

Appendix Figure 1. Principles of LCI.



LCI = linked color imaging. **Left.** The spectral characteristics of white fluorescence excited by a laser for white light and the short-wavelength laser. LCI expands and reduces color information simultaneously to intensify shades of red and white. **Right.** LCI enhances the contrast of red and white colors compared with a white light image.

Appendix Table 2. Patients With Previous Cancer, by Site

Site	WLI Group, *n*	LCI Group, *n*	Total, *n*
Head and neck	35	38	73
Esophagus	103	112	215
Stomach	362	351	713
Duodenum	2	3	5
Large intestine	38	30	68
Head and neck/esophagus	30	21	51
Head and neck/stomach	11	15	26
Head and neck/duodenum	1	–	1
Head and neck/large intestine	–	5	5
Esophagus/stomach	23	26	49
Esophagus/large intestine	8	4	12
Stomach/duodenum	–	2	2
Stomach/small intestine	1	–	1
Stomach/large intestine	7	13	20
Head and neck/esophagus/stomach	9	8	17
Head and neck/esophagus/large intestine	2	–	2
Head and neck/stomach/large intestine	–	1	1
Esophagus/stomach/large intestine	1	1	2
Head and neck/esophagus/stomach/large intestine	1	–	1
Total	634	630	1264

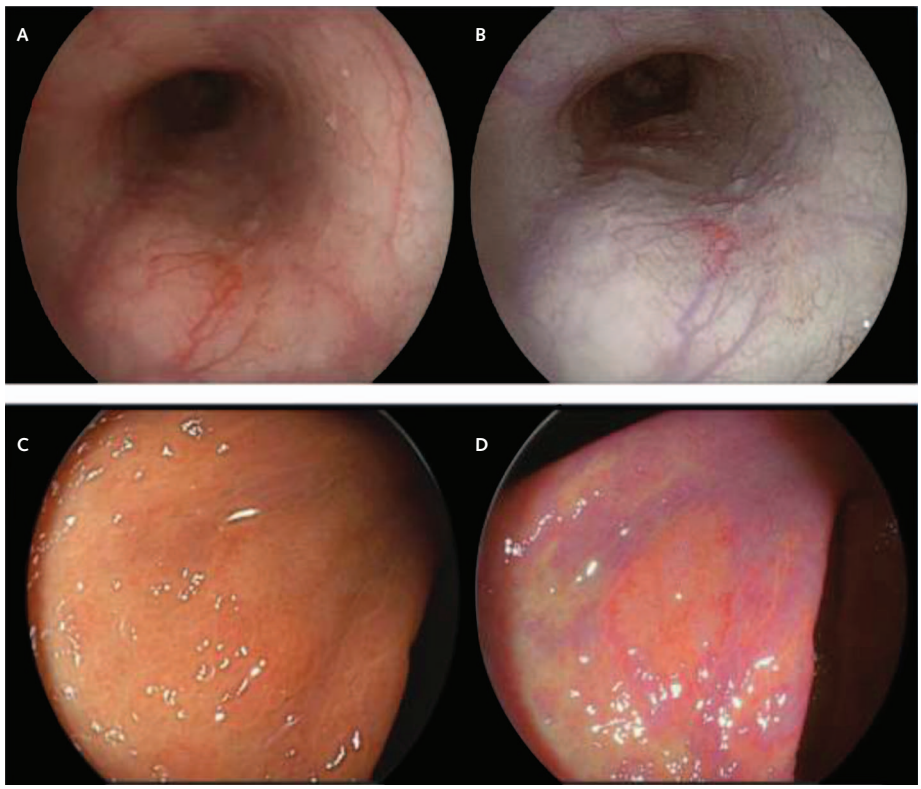
LCI = linked color imaging; WLI = white light imaging.

Appendix Table 3. Endoscopist-Specific Numbers of Examinations and Patients With Detected Tumors

Endoscopist	WLI Group		LCI Group		Total	
	Patients Examined, *n*	Detected Tumors, *n (%)*	Patients Examined, *n*	Detected Tumors, *n (%)*	Patients Examined, *n*	Detected Tumors, *n (%)*
1	120	5 (4.2)	111	16 (14.4)	231	21 (9.1)
2	74	7 (9.5)	72	13 (18.1)	146	20 (13.7)
3	97	8 (8.2)	100	7 (7.0)	197	15 (7.6)
4	10	2 (20.0)	17	3 (17.6)	27	5 (18.5)
5	34	1 (2.9)	32	3 (9.4)	66	4 (6.1)
6	19	1 (5.3)	25	3 (12.0)	44	4 (9.1)
7	40	1 (2.5)	57	2 (3.5)	97	3 (3.1)
8	19	1 (5.3)	20	2 (10.0)	39	3 (7.7)
9	9	0 (0)	10	3 (30.0)	19	3 (15.8)
10	29	1 (3.4)	28	1 (3.6)	57	2 (3.5)
11	18	2 (11.1)	13	0 (0)	31	2 (6.5)
12	14	0 (0)	16	2 (12.5)	30	2 (6.7)
13	8	2 (25.0)	5	0 (0)	13	2 (15.4)
14	21	1 (4.8)	28	0 (0)	49	1 (2.0)
15	15	1 (6.7)	17	0 (0)	32	1 (3.1)
16	9	0 (0)	12	1 (8.3)	21	1 (4.8)
17	9	0 (0)	8	1 (12.5)	17	1 (5.9)
18	7	0 (0)	4	1 (25.0)	11	1 (9.1)
19	6	1 (16.7)	5	0 (0)	11	1 (9.1)
20	8	1 (12.5)	1	0 (0)	9	1 (11.1)
21	4	1 (25.0)	4	0 (0)	8	1 (12.5)
22	3	0 (0)	2	1 (50.0)	5	1 (20.0)
23	2	0 (0)	2	1 (50.0)	4	1 (25.0)
24	36	0 (0)	35	0 (0)	71	0 (0)
25	24	0 (0)	20	0 (0)	44	0 (0)
26	14	0 (0)	9	0 (0)	23	0 (0)
27	6	0 (0)	12	0 (0)	18	0 (0)
28	11	0 (0)	6	0 (0)	17	0 (0)
29	8	0 (0)	7	0 (0)	15	0 (0)
30	6	0 (0)	9	0 (0)	15	0 (0)
31	5	0 (0)	7	0 (0)	12	0 (0)
32	5	0 (0)	7	0 (0)	12	0 (0)
33	4	0 (0)	5	0 (0)	9	0 (0)
34	7	0 (0)	2	0 (0)	9	0 (0)
35	1	0 (0)	7	0 (0)	8	0 (0)
36	6	0 (0)	2	0 (0)	8	0 (0)
37	3	0 (0)	4	0 (0)	7	0 (0)
38	5	0 (0)	2	0 (0)	7	0 (0)
39	4	0 (0)	3	0 (0)	7	0 (0)
40	5	0 (0)	1	0 (0)	6	0 (0)
41	4	0 (0)	1	0 (0)	5	0 (0)
42	2	0 (0)	3	0 (0)	5	0 (0)
43	3	0 (0)	2	0 (0)	5	0 (0)
44	3	0 (0)	2	0 (0)	5	0 (0)
45	2	0 (0)	2	0 (0)	4	0 (0)
46	3	0 (0)	1	0 (0)	4	0 (0)
47	1	0 (0)	2	0 (0)	3	0 (0)
48	1	0 (0)	2	0 (0)	3	0 (0)
49	1	0 (0)	2	0 (0)	3	0 (0)
50	1	0 (0)	2	0 (0)	3	0 (0)
51	1	0 (0)	1	0 (0)	2	0 (0)
52	2	0 (0)	0	0 (0)	2	0 (0)
53	1	0 (0)	0	0 (0)	1	0 (0)
54	0	0 (0)	1	0 (0)	1	0 (0)
55	0	0 (0)	1	0 (0)	1	0 (0)
56	1	0 (0)	0	0 (0)	1	0 (0)
57	1	0 (0)	0	0 (0)	1	0 (0)
58	0	0 (0)	1	0 (0)	1	0 (0)
Total	752	36 (4.8)	750	60 (8.0)	1502	96 (6.4)

LCI = linked color imaging; WLI = white light imaging.

Appendix Figure 2. Representative LCI images of early-stage cancer of the esophagus (*top*) and stomach (*bottom*).



LCI = linked color imaging; WLI = white light imaging. **Top.** Representative images of early-stage cancer of the esophagus in the WLI group (*A*) and LCI group (*B*). **Bottom.** Representative images of early-stage cancer of the stomach in the WLI group (*C*) and LCI group (*D*).

Appendix Table 4. Biopsied Lesions and Neoplastic Lesions in the Pharynx, Esophagus, and Stomach, by WLI and LCI (First Procedure in Each Group)

Site	WLI Group		LCI Group	
	Lesions, *n*	Neoplastic Lesions, *n (%)*	Lesions, *n*	Neoplastic Lesions, *n (%)*
Pharynx	6	2 (33.3)	17	7 (41.2)
Esophagus	21	10 (47.6)	39	18 (46.2)
Stomach	94	25 (26.6)	129	41 (31.8)
Total	121	37 (30.6)	185	66 (35.7)

LCI = linked color imaging; WLI = white light imaging.