

World Journal of *Gastroenterology*

World J Gastroenterol 2023 March 28; 29(12): 1765-1910



REVIEW

- 1765 Mitochondrial carnitine palmitoyltransferase-II dysfunction: A possible novel mechanism for nonalcoholic fatty liver disease in hepatocarcinogenesis
Yao M, Zhou P, Qin YY, Wang L, Yao DF
- 1779 Obesity and novel management of inflammatory bowel disease
Kim JH, Oh CM, Yoo JH
- 1795 Role of autoantibodies in the clinical management of primary biliary cholangitis
Rigopoulou EI, Bogdanos DP

MINIREVIEWS

- 1811 Artificial intelligence as a noninvasive tool for pancreatic cancer prediction and diagnosis
Faur AC, Lazar DC, Ghenciu LA
- 1824 New uses for an old remedy: Digoxin as a potential treatment for steatohepatitis and other disorders
Jamshed F, Dashti F, Ouyang X, Mehal WZ, Banini BA
- 1838 Autoimmune liver diseases and SARS-CoV-2
Sgamato C, Rocco A, Compare D, Minieri S, Marchitto SA, Maurea S, Nardone G
- 1852 Review of lymphoma in the duodenum: An update of diagnosis and management
Iwamuro M, Tanaka T, Okada H
- 1863 Comprehensive review on endoscopic ultrasound-guided tissue acquisition techniques for solid pancreatic tumor
Masuda S, Koizumi K, Shionoya K, Jinushi R, Makazu M, Nishino T, Kimura K, Sumida C, Kubota J, Ichita C, Sasaki A, Kobayashi M, Kako M, Haruki U

ORIGINAL ARTICLE

Basic Study

- 1875 Antihepatoma peptide, scolopentide, derived from the centipede scolopendra subspinipes mutilans
Hu YX, Liu Z, Zhang Z, Deng Z, Huang Z, Feng T, Zhou QH, Mei S, Yi C, Zhou Q, Zeng PH, Pei G, Tian S, Tian XF

Clinical Trials Study

- 1899 Linked color imaging vs Lugol chromoendoscopy for esophageal squamous cell cancer and precancerous lesion screening: A noninferiority study
Wang ZX, Li LS, Su S, Li JP, Zhang B, Wang NJ, Liu SZ, Wang SS, Zhang S, Bi YW, Gao F, Shao Q, Xu N, Shao BZ, Yao Y, Liu F, Linghu EQ, Chai NL

ABOUT COVER

Editorial Board of *World Journal of Gastroenterology*, Yirupaiahgar KS Viswanath, Professor, Consultant Surgeon (Upper GI, Laparoscopic and Robotic Surgery), Honorary Professor Teesside University, President Elect BBUGSS United Kingdom, MCh Programme Director, South Tees Hospitals NHS Foundation Trust, James Cook, University Hospital, Marton Road, Middlesbrough TS43BW, Cleveland, United Kingdom. ykviswanath@nhs.net

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (WJG, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 impact factor (IF) for WJG as 5.374; IF without journal self cites: 5.187; 5-year IF: 5.715; Journal Citation Indicator: 0.84; Ranking: 31 among 93 journals in gastroenterology and hepatology; and Quartile category: Q2. The WJG's CiteScore for 2021 is 8.1 and Scopus CiteScore rank 2021: Gastroenterology is 18/149.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Yu-Xi Chen*; Production Department Director: *Xu Guo*; Editorial Office Director: *Jia-Ru Fan*.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

March 28, 2023

COPYRIGHT

© 2023 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Clinical Trials Study

Linked color imaging vs Lugol chromoendoscopy for esophageal squamous cell cancer and precancerous lesion screening: A noninferiority study

Zi-Xin Wang, Long-Song Li, Song Su, Jin-Ping Li, Bo Zhang, Nan-Jun Wang, Sheng-Zhen Liu, Sha-Sha Wang, Shuai Zhang, Ya-Wei Bi, Fei Gao, Qun Shao, Ning Xu, Bo-Zong Shao, Yi Yao, Fang Liu, En-Qiang Linghu, Ning-Li Chai

Specialty type: Gastroenterology and hepatology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0

Grade B (Very good): B, B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

P-Reviewer: Abe Y, Japan; Tyakht AV, United Kingdom; Woromogo SH, Congo

Received: November 30, 2022

Peer-review started: November 30, 2022

First decision: December 20, 2022

Revised: December 29, 2022

Accepted: March 9, 2023

Article in press: March 9, 2023

Published online: March 28, 2023



Zi-Xin Wang, Long-Song Li, Song Su, Jin-Ping Li, Bo Zhang, Nan-Jun Wang, Sheng-Zhen Liu, Sha-Sha Wang, Shuai Zhang, Ya-Wei Bi, Fei Gao, Qun Shao, Ning Xu, Bo-Zong Shao, Yi Yao, Fang Liu, En-Qiang Linghu, Ning-Li Chai, Department of Gastroenterology, The First Medical Center of Chinese PLA General Hospital, Beijing 100853, China

Corresponding author: Ning-Li Chai, MD, Chief Physician, Professor, Department of Gastroenterology, The First Medical Center of Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China. csxlily@163.com

Abstract

BACKGROUND

Lugol chromoendoscopy (LCE) has served as a standard screening technique in high-risk patients with esophageal cancer. Nevertheless, LCE is not suitable for general population screening given its side effects. Linked color imaging (LCI) is a novel image-enhanced endoscopic technique that can distinguish subtle differences in mucosal color.

AIM

To compare the diagnostic performance of LCI with LCE in detecting esophageal squamous cell cancer and precancerous lesions and to evaluate whether LCE can be replaced by LCI in detecting esophageal neoplastic lesions.

METHODS

In this prospective study, we enrolled 543 patients who underwent white light imaging (WLI), LCI and LCE successively. We compared the sensitivity and specificity of LCI and LCE in the detection of esophageal neoplastic lesions. Clinicopathological features and color analysis of lesions were assessed.

RESULTS

In total, 43 patients (45 neoplastic lesions) were analyzed. Among them, 36 patients (38 neoplastic lesions) were diagnosed with LCI, and 39 patients (41 neoplastic lesions) were diagnosed with LCE. The sensitivity of LCI was similar to that of LCE (83.7% vs 90.7%, $P = 0.520$), whereas the specificity of LCI was greater

than that of LCE (92.4% *vs* 87.0%, $P = 0.007$). The LCI procedure time in the esophageal examination was significantly shorter than that of LCE [42 (34, 50) *s vs* 160 (130, 189) *s*, $P < 0.001$]. The color difference between the lesion and surrounding mucosa in LCI was significantly greater than that observed with WLI. However, the color difference in LCI was similar in different pathological types of esophageal squamous cell cancer.

CONCLUSION

LCI offers greater specificity than LCE in the detection of esophageal squamous cell cancer and precancerous lesions, and LCI represents a promising screening strategy for general populations.

Key Words: Linked color imaging; Lugol chromoendoscopy; Esophageal squamous cell cancer; Precancerous lesions; Color difference

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Lugol chromoendoscopy (LCE) has served as the standard screening technique in high-risk patients with esophageal cancer. Nevertheless, LCE can induce esophageal spasms and chest pain and is associated with the risk of aspiration and iodine allergy. Therefore, LCE is not suitable for general population screening. Linked color imaging (LCI) is a novel image-enhanced endoscopy that can distinguish subtle differences in mucosal color. In this study, we compared the use of LCI and LCE in the screening of esophageal neoplastic lesions. Based on our analysis, we found that LCI is more specific than LCE and represents a promising screening strategy.

Citation: Wang ZX, Li LS, Su S, Li JP, Zhang B, Wang NJ, Liu SZ, Wang SS, Zhang S, Bi YW, Gao F, Shao Q, Xu N, Shao BZ, Yao Y, Liu F, Linghu EQ, Chai NL. Linked color imaging *vs* Lugol chromoendoscopy for esophageal squamous cell cancer and precancerous lesion screening: A noninferiority study. *World J Gastroenterol* 2023; 29(12): 1899-1910

URL: <https://www.wjgnet.com/1007-9327/full/v29/i12/1899.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v29.i12.1899>

INTRODUCTION

Esophageal cancer is the seventh most common cancer and the sixth leading cause of cancer-related deaths worldwide[1]. Most patients with esophageal cancer have progressed to an advanced stage when diagnosed, with poor quality of life and an overall 5-year survival rate of less than 20%[2,3]. Esophageal squamous cell carcinoma (ESCC) is the most common form of esophageal cancer worldwide, representing greater than 85% of all esophageal cancer cases[4,5]. Curative resection using endoscopic mucosal resection or endoscopic submucosal dissection is possible for lesions with high-grade intraepithelial neoplasia and most T1 tumors, offering less trauma, faster recovery and fewer complications[6]. Therefore, early diagnosis is critical for treatment success and prognostic improvement. Early identification and timely intervention of esophageal cancer or precancerous lesions are of great significance to delay the progression of the disease, improve the prognosis and improve the quality of life.

However, under white light imaging (WLI) endoscopy, early neoplastic lesions are easily missed due to the presence of small lesion areas and subtle differences in the surrounding mucosa color[7]. Historically, Lugol chromoendoscopy (LCE) has served as the standard diagnostic technique given its higher detection rate[8-12]. However, its specificity is low due to light staining under conditions of inflammation, which has been demonstrated in previous studies[13-15]. Furthermore, LCE occasionally induces esophageal spasms and chest pain and is associated with the risk of aspiration and iodine allergy[16,17].

With the advent of image-enhanced endoscopy, many studies have confirmed its efficacy in diagnosing upper gastrointestinal neoplasms[13,18]. The LASEREO system (Fujifilm Corporation, Tokyo, Japan), a new linked color imaging (LCI) technology, was recently developed. LCI images are illuminated with white light and short wavelength narrow-band light in an appropriate proportion simultaneously to realize the simultaneous expansion and contraction of colors. This procedure facilitates enhancement of the red and white colors and makes it easier for the operators to identify the subtle differences in mucosal color[18-21]. In our clinical work, it was found that LCI significantly improved the ability to identify lesions. In a large-scale randomized comparative study, Ono *et al*[20] reported the superiority of LCI over WLI in detecting neoplastic lesions in the upper gastrointestinal tract. Previous studies reported the usefulness of LCI for esophageal neoplasm detection and

assessments of invasive depth[20-24]. Although Yi *et al*[25] compared LCI and LCE in the diagnosis of multiple primary esophageal cancers, no prospective study has compared the diagnosability of LCI with LCE in screening esophageal neoplastic lesions to date. Therefore, we conducted a prospective noninferiority study to compare the efficacy of non-magnifying LCI and LCE in detecting and diagnosing ESCC and precancerous lesions. We evaluated whether LCE can be replaced by LCI in detecting esophageal neoplastic lesions for the general population.

MATERIALS AND METHODS

Study design

This was a single-center, prospective, registered clinical study (No. ChiCTR2100045636) conducted at the First Medical Center of Chinese PLA General Hospital that compared the detection of ESCC and precancerous lesions using LCI *vs* LCE after a conventional white light examination. Endoscopic biopsy is considered the gold standard for ESCC detection. The study was approved by the medical ethics committee of the Chinese PLA General Hospital (Beijing, China), and informed consent forms were obtained from all patients.

Patients

The regional screening studies of esophageal cancer in China revealed that endoscopic screening starting at 40 years of age was cost-effective[26,27]. We recommended 40 years as the beginning age for screening in the Chinese consensus[28]. The following inclusion criteria were employed: (1) Age > 40-year-old; and (2) Provision of written consent to participate. The exclusion criteria were as follows: (1) Contraindication for upper gastrointestinal endoscopy or general anesthesia; (2) Iodine allergy or hyperthyroidism; and (3) Previous surgical resection or chemotherapy, radiotherapy or chemoradiotherapy for ESCC (as these procedures may influence the mucosal surface, which is important for detecting these lesions).

Diagnostic strategies

This study used an upper EG-590WR scope (Fujifilm) for gastroscopy. The specific examination procedure was performed as follows. First, WLI examination was performed, and all detected lesions were described. Second, LCI examination was performed, and all lesions detected were recorded in the report (another researcher) but not biopsied immediately to avoid bleeding that could influence the Lugol examination. Third, LCE was performed (2% Lugol dye was spread over the entire esophagus using a spray catheter except near the upper esophageal sphincter given the risk of aspiration), and we biopsied the suspected lesions detected by LCE. Finally, vitamin C solution was used to discolor the Lugol-stained mucosa[29], and lesions suspected only in LCI mode were biopsied based on the recorded location. All suspected lesions were biopsied, and the modality (only LCI, only LCE, or both LCI and LCE) that detected each lesion was indicated in the report. A flow chart of the study is described in Figure 1. All endoscopic operators were experienced and had completed at least 1000 endoscopies. The diagnosis modality (LCI or/and LCE), size, location and macroscopic type (Paris classification[30]) of each detected lesion were recorded and described after examination.

Outcome

The diagnostic criteria for intraepithelial neoplasia and ESCC proposed by the Vienna Classification are as follows: Low-grade intraepithelial neoplasia (LGIN); high-grade intraepithelial neoplasia (HGIN), ESCC and negative for neoplasia, including chronic esophagitis[31]. The primary outcome was the sensitivity and specificity of the diagnostic strategies to detect squamous cell neoplastic lesions (LGIN, HGIN and/or ESCC) according to histology. Endoscopically suspicious ESCC lesions and precancerous lesions were defined as follows: (1) The presence of a reddish color change with a rough mucosal surface in WLI (Figure 2A); (2) The presence of a well-demarcated red or red-orange color region in LCI (Figure 2B)[21,22]; and (3) The presence of a well-demarcated unstained area ≥ 5 mm in diameter or a pink color area after iodine staining given that a Lugol-voiding lesion is more likely to be neoplastic with increasing size (Figure 2C)[32,33].

All suspected lesions were pathologically evaluated by biopsy to determine their neoplastic nature. If the lesion was confirmed to be neoplastic, it was a true positive for the detection modality. Conversely, for non-neoplastic lesions, an unconfirmed suspected lesion was defined as a false positive for the detection modality.

Major outcomes included sensitivity and specificity. The secondary outcome was procedure time. It was possible to determine the length of the imaging operation using a clock linked to the endoscopic equipment. The LCI procedure time was defined as the total examination time from the epiglottis to the dentate line in the image files. The LCE procedure time was defined as the examination time from spraying Lugol dye to complete discoloration.

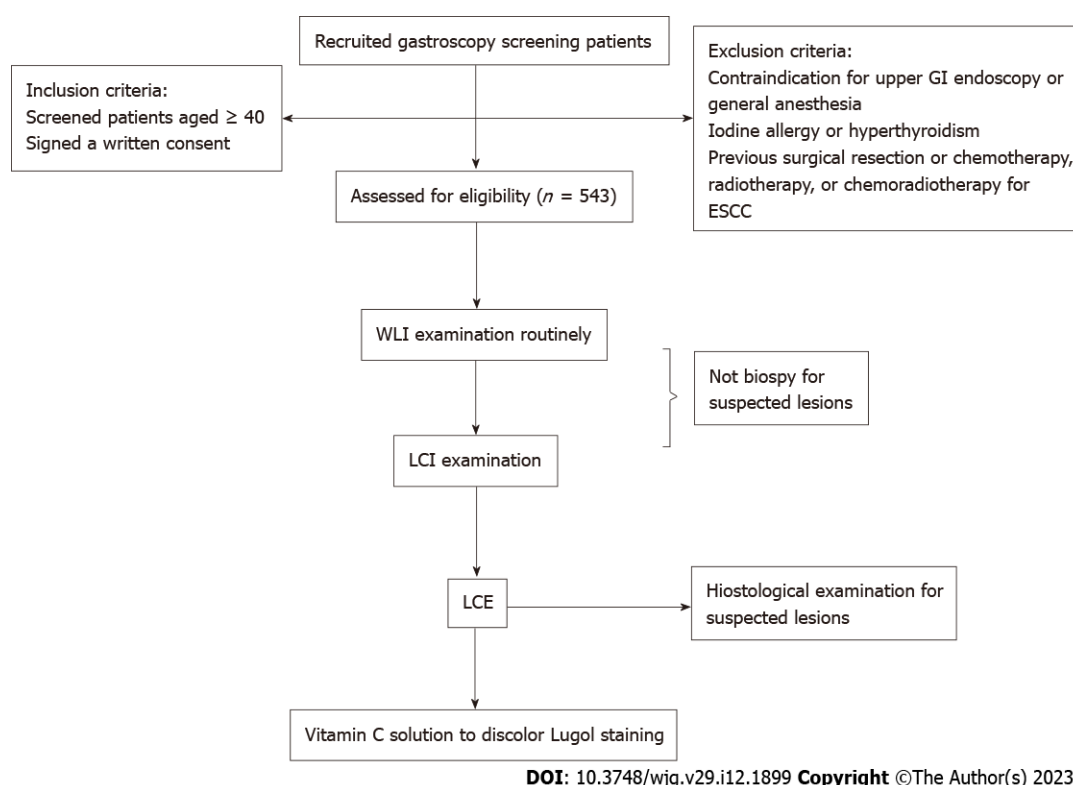


Figure 1 Flow chart of study design. ESCC: Esophageal squamous cell carcinoma; GI: Gastrointestinal; LCE: Lugol chromoendoscopy; LCI: Linked color imaging; WLI: White light imaging.

Sample size

In this study, we calculated the required sample size for a noninferiority test using the PASS 15.0.5 sample size software (NCSS, LLC, Kaysville, UT, United States). We regarded LCE as the reference endoscopy technique, and sensitivity was assumed to be 90.0% [13,14]. A sensitivity of 80.0% would be a clinically adequate diagnostic value for screening endoscopy for ESCC. The sample size required was 535 patients using the Z test with pooled variance for a statistical power of 90% with statistical significance defined as $P < 0.05$ ($\alpha = 0.05$ and $\beta = 0.10$).

Color analysis

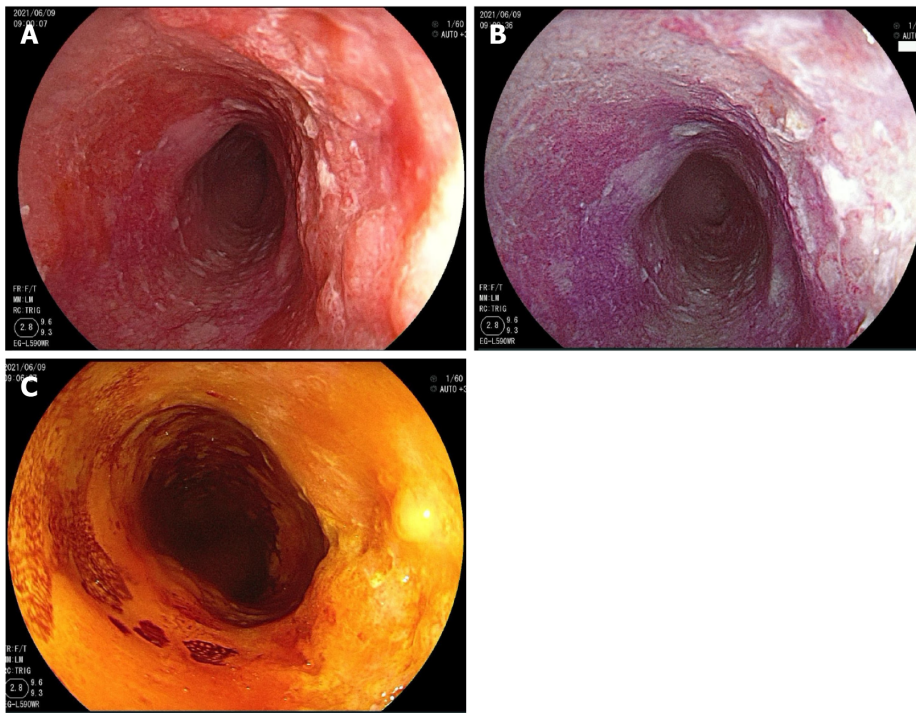
Color analysis was performed using Adobe Photoshop CC2017 (Adobe Systems Inc., San Jose, CA, United States). First, regions of interest of the lesion mucosa and surrounding mucosa were selected in WLI and LCI, separately (Figure 3). Second, the Commission International de l'Eclairage - $L^*a^*b^*$ color space was used to evaluate the mean color value in the regions of interest [34]. 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; range: 128 to + 127) were used to define the color value. In Photoshop, L^* , a^* and b^* represent color scores (Lab color unit). Third, the color difference between the lesion and the surrounding mucosa (ΔE) was represented by the distance connecting the two points:

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

To reduce the influence of color difference depending on imaging conditions, we chose similar distance and angle images in each mode to calculate color values. We calculated the ΔE of each image in LCI and WLI. In addition, we calculated the ΔE of different neoplastic pathologies in LCI and compared them.

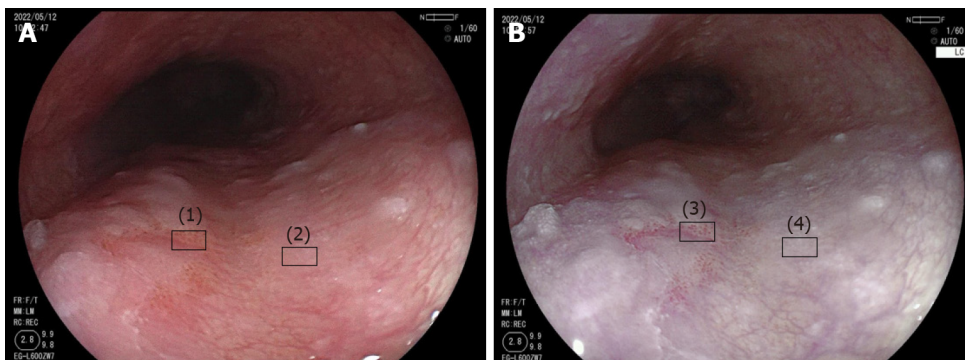
Statistical analysis

All analyses were performed using SPSS 26.0 statistical software (IBM Corp., Armonk, NY, United States). The characteristics and diagnostic yields of patients were presented as percentages (%) or medians (interquartile range), and the color difference variables were expressed as the mean \pm SD. Continuous variables were compared using the student's t -test or the Mann-Whitney U test, whereas categorical variables were compared using Pearson's χ^2 test or Fisher's exact test. A two-tailed P value of < 0.05 was considered statistically significant. The statistical methods of this study were reviewed by the staff of the Department of Epidemiology and Statistics from the First Medical Center of PLA General Hospital (Beijing, China).



DOI: 10.3748/wjg.v29.i12.1899 Copyright ©The Author(s) 2023.

Figure 2 A single esophageal squamous cell carcinoma lesion visualized under the three detection methods. A: Under white light imaging; B: Under linked color imaging; C: Under Lugol chromoendoscopy.



DOI: 10.3748/wjg.v29.i12.1899 Copyright ©The Author(s) 2023.

Figure 3 Method to measure the color difference between neoplastic and non-neoplastic lesions detected by white light imaging and linked color imaging. A: Neoplastic lesion (1) and non-neoplastic lesion (2) detected by white light imaging; B: Neoplastic lesion (3) and non-neoplastic lesion (4) detected by linked color imaging.

RESULTS

Participants

From March 2021 to May 2022, a total of 543 patients were enrolled in our study (Figure 1). Among them, a total of 141 suspected lesions were identified in 115 patients. Of these lesions, 45 neoplastic lesions (17 ESCC, 3 HGIN and 25 LGIN) were histologically confirmed in 43 (7.8%) patients (Table 1). Among the 45 lesions, 38 lesions (17 ESCC, 3 HGIN and 18 LGIN) were endoscopically suspicious during LCI examination; further, 41 lesions (17 ESCC, 3 HGIN and 21 LGIN) were endoscopically suspicious during LCE examination. Regarding the diagnostic modality of the 45 lesions, 34 (75.6%) lesions were identified by LCI and LCE compared to 4 (8.9%) lesions that were detected only by LCI and 7 (15.6%) lesions that were detected only by LCE.

Diagnostic performance of LCI and LCE for neoplastic lesions

In LCI mode, 74 suspected lesions underwent histological examination, and 38 lesions were confirmed histologically in 36 patients. In LCE mode, 104 suspected lesions were detected, and 41 lesions were

Table 1 Clinicopathological features of the patients

Item	<i>n</i>	% (<i>n/n</i> total)
Patients with suspected lesions ¹	115	21.2 (115/543)
Inflammation	72	13.2
LGIN	25	4.6
HGIN	3	0.5
ESCC	15	2.7
Suspected lesions, including non-neoplastic	141	-
Neoplastic lesions ²	45	31.9 (45/141)
LGIN	25	17.7 (25/141)
HGIN	3	2.1 (3/141)
ESCC	17	12.1 (17/141)
Neoplastic lesions detected with LCI		
LGIN	18	72.0 (18/25)
HGIN	3	100 (3/3)
ESCC	17	100 (17/17)
Neoplastic lesions detected with LCE		
LGIN	21	84.0 (21/25)
HGIN	3	100 (3/3)
ESCC	17	100 (17/17)
Neoplastic lesions detected by different diagnosis modality		
Only LCI	4	8.9 (4/45)
Only LCE	7	15.6 (7/45)
Both LCI and LCE	34	75.6 (34/45)
Neoplastic lesions per patient, mean (SD)	0.08 (0.29)	

¹Suspected lesions included neoplastic lesions and false positives (lesions detected but not confirmed to be neoplastic after histological examination).

²Neoplastic lesions confirmed by histological examination.

ESCC: Esophageal squamous cell carcinoma; HGIN: High-grade intraepithelial neoplasia; LCE: Lugol chromoendoscopy; LCI: Linked color imaging; LGIN: Low-grade intraepithelial neoplasia; SD: Standard deviation.

histologically confirmed in 39 patients. In [Table 2](#), the sensitivity, specificity, positive predictive value and negative predictive value for LCI for the diagnosis of ESCC/HGIN/LGIN were 83.7%, 92.4%, 48.6% and 98.5%, respectively. The sensitivity, specificity, positive predictive value and negative predictive value for LCE were 90.7%, 87.0%, 37.5% and 99.1%, respectively. No significant differences in sensitivity, positive predictive value and negative predictive value were noted between LCI and LCE. However, the specificity of LCI was significantly higher than that of LCE (92.4% *vs* 87.0%, *P* = 0.0023).

Characteristics of the neoplastic lesions detected by LCI and LCE

The characteristics of the neoplastic lesions detected by LCI and LCE of the respective comparison groups are shown in [Table 3](#). No significant differences in lesion location, size, morphologic type or pathology were noted between the two modality groups. However, the procedure time was significantly shorter for the LCI group compared with the LCE group [42 (34, 50) *s vs* 160 (130, 189) *s*, *P* < 0.001].

All detected neoplastic lesions were further divided into three subgroups according to the different diagnosis modalities: LCI only group (detected by LCI only, *n* = 4 lesions), LCE only group (detected by LCE only, *n* = 7 lesions), and LCI + LCE group (detected by both LCI and LCE, *n* = 34 lesions). We compared the clinicopathological features of the three groups in [Supplementary Table 1](#). The lesion location, morphologic type and pathology were comparable among the three groups. However, the lesion sizes of the three groups were significantly different: 20 (55.8%) lesions in the LCI + LCE group were > 20 mm; 3 (75%) lesions in the LCI only group were ≤ 10 mm; and 7 (100%) lesions in the LCE only group were ≤ 10 mm (*P* = 0.016). We further compared the lesion size in the LCI only group and

Table 2 Esophageal neoplastic lesions (non-inflammation) detected using linked color imaging and Lugol chromoendoscopy

Parameter	LCI	LCE	P value
Sensitivity	83.7 (36/43)	90.7 (39/43)	0.520
Specificity	92.4 (462/500)	87.0 (435/500)	0.007 ¹
PPV	48.6 (36/74)	37.5 (39/104)	0.166
NPV	98.5 (462/469)	99.1 (435/439)	0.549

¹*P* < 0.01.Data are presented as % (*n*/*n* total). LCE: Lugol chromoendoscopy; LCI: Linked color imaging; NPV: Negative predictive value; PPV: Positive predictive value.**Table 3 Clinicopathological features of neoplastic lesions (non-inflammation) detected by linked color imaging and Lugol chromoendoscopy, *n* (%)**

Item	Detected by LCI, <i>n</i> = 36 patients/38 lesions	Detected by LCE, <i>n</i> = 39 patients/41 lesions	P value
Lesion location			0.969
Upper	3 (7.9)	3 (7.3)	
Middle	11 (28.9)	11 (26.8)	
Lower	24 (63.2)	27 (65.9)	
Morphologic type			0.902
I	1 (2.6)	1 (2.4)	
IIa	9 (23.7)	8 (19.5)	
IIb	18 (47.4)	24 (58.5)	
IIc	9 (23.7)	7 (17.1)	
III	1 (2.6)	1 (2.4)	
Size in mm			0.814
≤ 10	14 (36.8)	18 (43.9)	
10-20	3 (7.9)	3 (7.3)	
> 20	21 (55.3)	20 (48.8)	
Pathology			0.998
LGIN	18 (47.4)	21 (51.2)	
HGIN	3 (7.9)	3 (7.3)	
ESCC			
EP/LPM	3 (7.9)	3 (7.3)	
MM/SM1	1 (2.6)	1 (2.4)	
≥ SM2	13 (34.2)	13 (31.7)	
Procedure time (s), median (IQR)	42 (34, 50)	160 (130, 189)	< 0.001 ¹

¹*P* value < 0.01.

EP: Epithelial; ESCC: Esophageal squamous cell carcinoma; HGIN: High-grade intraepithelial neoplasia; IQR: Interquartile range; LCE: Lugol chromoendoscopy; LCI: Linked color imaging; LGIN: Low-grade intraepithelial neoplasia; LPM: Lamina propria mucosa; MM: Muscularis mucosa; SM1: Submucosa invading ≤ 200 μm below the inferior margin of the muscularis mucosa; SM2: Submucosa invading > 200 μm below the inferior margin of the muscularis mucosa.

LCE only group, and the difference was not statistically significant (*P* = 0.364).**Color analysis**Of the 45 neoplastic lesions, 30 lesions had endoscopic images with clear visibility. Color analysis was conducted in the 30 lesions. **Supplementary Table 2** compares the color difference between the lesion

and surrounding mucosa in WLI and LCI. We found that the ΔE between the lesions and the surrounding mucosa was significantly higher in LCI compared with WLI (21.20 ± 9.79 vs 15.92 ± 7.50 , respectively, $P = 0.023$). For the three-dimensional color parameters of $L^*a^*b^*$, Δa^* was higher in LCI than in WLI (12.43 ± 10.00 vs 4.97 ± 6.96 , respectively, $P = 0.001$), and ΔL^* and Δb^* were similar in LCI and WLI. We further analyzed the color difference between the lesion and surrounding mucosa in different neoplastic pathologies (LGIN, HGIN and ESCC) in LCI mode, as shown in [Supplementary Table 3](#). However, no significant differences in ΔE , ΔL^* , Δa^* and Δb^* were noted among the three pathological types.

DISCUSSION

In this prospective study, we demonstrated that the sensitivity and specificity of LCI to detect ESCC and/or precancerous lesions (LGIN or/and HGIN) are acceptable. The specificity of LCI is higher than that of LCE, and the differences in sensitivity between the two modes were not obvious.

Previous studies have reported the utility of LCE in the detection of esophageal cancer[7,10-12]. LCE has served as the reference technique in patients at high risk for esophageal cancer[8,9]. Nevertheless, LCE is not suitable for general population screening given its side effects[16,17]. As a type of enhanced endoscopy, some studies have shown that narrow-band imaging is comparable to LCE in detecting esophageal cancer due to its excellent sensitivity and specificity[13-15]. Narrow-band imaging is typically combined with magnifying endoscopy, and the requirements for hospitals and operators are relatively high. LCI is a novel enhanced endoscopic technique, and Ono *et al*[20] reported that the detection rate of LCI in the diagnosis of neoplastic lesions in the upper gastrointestinal tract is 1.67 times higher than that of WLI. Yi *et al*[25] compared LCI and LCE in the detection of multiple primary esophageal cancers in primary ESCC patients and found that both modalities exhibited great value for multiple primary esophageal cancers. However, no study has compared their screening ability. To the best of our knowledge, this was the first prospective study to compare the effectiveness of LCI and LCE in screening esophageal cancer and precancerous lesions.

The present results showed that LCI is significantly more specific than LCE (92.4% vs 87.0%, $P = 0.0023$), and both modes exhibited high sensitivity for detecting neoplastic lesions (LGIN/HGIN/ESCC) (83.7% vs 90.7%, $P = 0.520$). The lesions were all pathologically diagnosed as LGIN (7 lesions in LCI and 4 in LCE). Therefore, our study results were consistent with previously published data reporting that the sensitivity of narrow-band imaging and Lugol for the diagnosis of ESCC and/or HGIN was approximately 100%[13,14]. The LCI only group included a lesion approximately 4 cm in length, and no unstained areas were observed. Based on the endoscopic findings, we thought that it was an erosive mucosal lesion caused by gastric acid reflux. Our results indicate that the capability of LCI to detect neoplastic lesions is acceptable.

The LCI technique is convenient for clinical endoscopists to use with the Fujifilm system because the imaging modes can easily be switched during the examination. Thus, the process is not as time-consuming as iodine staining. In our research, the median LCI procedure time was significantly shorter than for LCE (42 s vs 160 s, $P < 0.001$). In addition, Lugol solution can irritate the mucosa and may cause many side effects (chemical esophagitis, laryngitis, bronchopneumonia, chest pain, esophagospasm, gastritis and hypersensitivity)[16,17]. In clinical practice, the upper end of the Lugol staining site is generally less than 20 cm from the incisor given the high risk of solution aspiration. Therefore, it is difficult to detect cervical esophageal lesions, which reduces the detection of synchronous or metachronous neoplastic lesions. Therefore, the LCI technique is more useful for the diagnosis of ESCC or precancerous lesions given the mild mucosal irritation.

After color analysis, we found that the color difference between the lesion and the surrounding mucosa was greater for LCI compared with WLI. The results demonstrated that the lesion was more visible in LCI mode, which is consistent with previous studies[18,19,21,22]. Kobayashi *et al*[21] investigated the relationship between color information and the invasion depth of ESCC in LCI mode. They found that the color difference was greater in muscularis mucosa/submucosa invading ≤ 200 μm below the inferior margin of the muscularis mucosa or deeper lesions compared with epithelium and lamina propria mucosa lesions using LCI. However, they did not compare the color differences between ESCC and precancerous lesions. In our study, we further compared the color difference of different neoplastic pathologies in LCI mode, and the differences among LGIN, HGIN and ESCC were not significant. Notably, Tsunoda *et al*[35] reported a case using LCI and blue laser imaging with Lugol staining to provide an accurate diagnosis of ESCC and squamous intraepithelial neoplasia. Therefore, whether LCI and blue laser imaging combined with Lugol staining can be used to evaluate esophageal neoplastic lesions before endoscopic treatment deserves further study.

There are some limitations in our study. First, the number of lesions, especially neoplastic lesions, was low. Second, LCI and LCE can be performed sequentially during the same endoscopy procedure, but it is impossible to perform them in the reverse order. Thus, we were unable to perform a random crossover trial. Third, the images obtained in this study included two arbitrary regions of interest in the lesion mucosa and surrounding mucosa, which may have sampling errors and affected the

measurement results. However, for the WLI and LCI modes, we choose similar distance and angle images to calculate color values to reduce the influence of color differences based on various conditions. In the future, we need to conduct a multicenter study and collect more neoplastic lesions to further evaluate the usefulness of LCI. Further evaluation of the validity of LCI in diagnosing the depth of invasion of ESCC is also warranted.

CONCLUSION

Our study confirmed that LCI is efficient and specific for the surveillance of ESCC without causing discomfort. In the future, LCI, as a promising screening strategy, could replace LCE in the screening of esophageal neoplastic lesions in the general population.

ARTICLE HIGHLIGHTS

Research background

Lugol chromoendoscopy (LCE) has served as a standard screening technique in high-risk patients with esophageal cancer. Nevertheless, LCE is not suitable for the general population screening given its side effects. Linked color imaging (LCI) is a novel image-enhanced endoscopic technique that can distinguish subtle differences in mucosal color. It would be beneficial for the general population if LCE can provide similar diagnostic performance to LCI.

Research motivation

We compared the diagnostic performance of LCI with LCE in detecting esophageal squamous cell carcinoma (ESCC) and precancerous lesions. If LCI can replace LCE in detecting esophageal neoplastic lesions, it would be useful for esophageal screening in the general population.

Research objectives

As a novel image-enhanced endoscopic technique, LCI has been confirmed to be superior to white light imaging (WLI) in detecting neoplastic lesions in the upper gastrointestinal tract. We aimed to confirm that the diagnostic performance of LCI is comparable to LCE for the surveillance of ESCC.

Research methods

This was a single-center, prospective, registered clinical study. In this noninferiority study, we prospectively enrolled 543 patients who underwent WLI, LCI and LCE successively. We compared the sensitivity and specificity of LCI and LCE in the detection of esophageal neoplastic lesions. We further used L*a*b* color space to evaluate the color differences of LCI.

Research results

In total, 43 patients were analyzed. The sensitivity of LCI was similar to that of LCE, whereas the specificity of LCI was greater than that of LCE. The LCI procedure time in the esophageal examination was significantly shorter than that of LCE. However, the color difference in LCI was similar in different pathological types.

Research conclusions

Our study showed that LCI is efficient and specific for the surveillance of ESCC without causing discomfort. In the future, LCI, as a promising screening strategy, could replace LCE in the screening of esophageal neoplastic lesions in the general population.

Research perspectives

Because of the low detection rate of esophageal cancer, we were only able to enroll a limited number of neoplastic lesions. In the future, we need to conduct a multicenter study and collect more neoplastic lesions to further evaluate the usefulness of LCI. Further evaluation of the validity of LCI in diagnosing the depth of invasion of ESCC is also warranted.

ACKNOWLEDGEMENTS

We thank our peer reviewers for the insightful and thorough suggestions on this manuscript.

FOOTNOTES

Author contributions: Wang ZX and Li LS contributed equally to this work; Chai NL and Linghu EQ contributed to study conception and design; Wang ZX and Li LS contributed to manuscript drafting; Li LS, Su S, Li JP, Wang NJ, Zhang B, Liu SZ, Zhang S, Wang SS, Bi YW, Gao F, Shao Q, Xu N, Shao BZ, Yao Y, and Liu F contributed to data acquisition; Chai NL, Linghu EQ, Li LS and Su S contributed to critical revision of the article for important intellectual content; and all authors issued final approval for the version to be submitted.

Supported by the National Natural Science Foundation of China, No. 81270564 and 82100697.

Institutional review board statement: The study was reviewed and approved by the ethics committee of the Chinese PLA general hospital (Approval No. of Ethics Committee: S2021-145-01).

Clinical trial registration statement: This study was registered in the Chinese clinical trial database (chictr.org) with the number ChiCTR2100045636.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Zi-Xin Wang 0000-0003-3929-3448; Long-Song Li 0000-0002-4000-7501; Song Su 0000-0002-3199-7865; Jin-Ping Li 0000-0003-4891-922X; Bo Zhang 0000-0002-4333-0750; Nan-Jun Wang 0000-0002-6061-4798; Sheng-Zhen Liu 0000-0001-9206-8173; Sha-Sha Wang 0000-0001-6916-7552; Shuai Zhang 0000-0003-3748-5438; Ya-Wei Bi 0000-0003-3762-5920; Fei Gao 0000-0002-9444-4168; Qun Shao 0000-0001-6503-6133; Ning Xu 0000-0002-7770-8731; Bo-Zong Shao 0000-0002-2621-0669; Yi Yao 0000-0001-6976-3418; Fang Liu 0000-0002-2013-9881; En-Qiang Linghu 0000-0003-4506-7877; Ning-Li Chai 0000-0002-6791-5817.

S-Editor: Wang JJ

L-Editor: A

P-Editor: Wang JJ

REFERENCES

- Erratum: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2020; **70**: 313 [PMID: 32767693 DOI: 10.3322/caac.21609]
- Ciocirlan M, Lapalus MG, Hervieu V, Souquet JC, Napoléon B, Scoazec JY, Lefort C, Saurin JC, Ponchon T. Endoscopic mucosal resection for squamous premalignant and early malignant lesions of the esophagus. *Endoscopy* 2007; **39**: 24-29 [PMID: 17252456 DOI: 10.1055/s-2006-945182]
- Merkow RP, Bilimoria KY, Keswani RN, Chung J, Sherman KL, Knab LM, Posner MC, Bentrem DJ. Treatment trends, risk of lymph node metastasis, and outcomes for localized esophageal cancer. *J Natl Cancer Inst* 2014; **106** [PMID: 25031273 DOI: 10.1093/jnci/dju133]
- Morgan E, Soerjomataram I, Rumgay H, Coleman HG, Thrift AP, Vignat J, Laversanne M, Ferlay J, Arnold M. The Global Landscape of Esophageal Squamous Cell Carcinoma and Esophageal Adenocarcinoma Incidence and Mortality in 2020 and Projections to 2040: New Estimates From GLOBOCAN 2020. *Gastroenterology* 2022; **163**: 649-658.e2 [PMID: 35671803 DOI: 10.1053/j.gastro.2022.05.054]
- Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, Bray F. Global Burden of 5 Major Types of Gastrointestinal Cancer. *Gastroenterology* 2020; **159**: 335-349.e15 [PMID: 32247694 DOI: 10.1053/j.gastro.2020.02.068]
- Obermannová R, Alsina M, Cervantes A, Leong T, Lordick F, Nilsson M, van Grieken NCT, Vogel A, Smyth EC; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2022; **33**: 992-1004 [PMID: 35914638 DOI: 10.1016/j.annonc.2022.07.003]
- Hashimoto CL, Iriya K, Baba ER, Navarro-Rodriguez T, Zerbini MC, Eisig JN, Barbuti R, Chinzon D, Moraes-Filho JP. Lugol's dye spray chromoendoscopy establishes early diagnosis of esophageal cancer in patients with primary head and

- neck cancer. *Am J Gastroenterol* 2005; **100**: 275-282 [PMID: 15667482 DOI: 10.1111/j.1572-0241.2005.30189.x]
- 8 **Bisschops R**, Arcia M, Coron E, Dobru D, Kaskas B, Kuvaev R, Pech O, Ragunath K, Weusten B, Familiari P, Domagk D, Valori R, Kaminski MF, Spada C, Bretthauer M, Bennett C, Senore C, Dinis-Ribeiro M, Rutter MD. Performance measures for upper gastrointestinal endoscopy: a European Society of Gastrointestinal Endoscopy (ESGE) Quality Improvement Initiative. *Endoscopy* 2016; **48**: 843-864 [PMID: 27548885 DOI: 10.1055/s-0042-113128]
 - 9 **Hirota WK**, Zuckerman MJ, Adler DG, Davila RE, Egan J, Leighton JA, Qureshi WA, Rajan E, Fanelli R, Wheeler-Harbaugh J, Baron TH, Faigel DO; Standards of Practice Committee, American Society for Gastrointestinal Endoscopy. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006; **63**: 570-580 [PMID: 16564854 DOI: 10.1016/j.gie.2006.02.004]
 - 10 **Shiozaki H**, Tahara H, Kobayashi K, Yano H, Tamura S, Imamoto H, Yano T, Oku K, Miyata M, Nishiyama K. Endoscopic screening of early esophageal cancer with the Lugol dye method in patients with head and neck cancers. *Cancer* 1990; **66**: 2068-2071 [PMID: 1699649 DOI: 10.1002/1097-0142(19901115)66:10<2068::aid-cnrcr2820661005>3.0.co;2-w]
 - 11 **Muto M**, Hironaka S, Nakane M, Boku N, Ohtsu A, Yoshida S. Association of multiple Lugol-voiding lesions with synchronous and metachronous esophageal squamous cell carcinoma in patients with head and neck cancer. *Gastrointest Endosc* 2002; **56**: 517-521 [PMID: 12297767 DOI: 10.1067/mge.2002.128104]
 - 12 **Shimizu Y**, Tukagoshi H, Fujita M, Hosokawa M, Kato M, Asaka M. Endoscopic screening for early esophageal cancer by iodine staining in patients with other current or prior primary cancers. *Gastrointest Endosc* 2001; **53**: 1-5 [PMID: 11154480 DOI: 10.1067/mge.2001.111387]
 - 13 **Morita FH**, Bernardo WM, Ide E, Rocha RS, Aquino JC, Minata MK, Yamazaki K, Marques SB, Sakai P, de Moura EG. Narrow band imaging versus lugol chromoendoscopy to diagnose squamous cell carcinoma of the esophagus: a systematic review and meta-analysis. *BMC Cancer* 2017; **17**: 54 [PMID: 28086818 DOI: 10.1186/s12885-016-3011-9]
 - 14 **Gruner M**, Denis A, Masliah C, Amil M, Metivier-Cesbron E, Luet D, Kaasis M, Coron E, Le Rhun M, Lecleire S, Antonietti M, Legoux JL, Lefrou L, Renkes P, Tarreiras AL, Balian P, Rey P, Prost B, Cellier C, Rahmi G, Samaha E, Fratte S, Guerrier B, Landel V, Touzet S, Ponchon T, Pioche M. Narrow-band imaging versus Lugol chromoendoscopy for esophageal squamous cell cancer screening in normal endoscopic practice: randomized controlled trial. *Endoscopy* 2021; **53**: 674-682 [PMID: 32698233 DOI: 10.1055/a-1224-6822]
 - 15 **Nagami Y**, Tominaga K, Machida H, Nakatani M, Kameda N, Sugimori S, Okazaki H, Tanigawa T, Yamagami H, Kubo N, Shiba M, Watanabe K, Watanabe T, Iguchi H, Fujiwara Y, Ohira M, Hirakawa K, Arakawa T. Usefulness of non-magnifying narrow-band imaging in screening of early esophageal squamous cell carcinoma: a prospective comparative study using propensity score matching. *Am J Gastroenterol* 2014; **109**: 845-854 [PMID: 24751580 DOI: 10.1038/ajg.2014.94]
 - 16 **Sreedharan A**, Rembacken BJ, Rotimi O. Acute toxic gastric mucosal damage induced by Lugol's iodine spray during chromoendoscopy. *Gut* 2005; **54**: 886-887 [PMID: 15888800 DOI: 10.1136/gut.2004.061739]
 - 17 **Park JM**, Seok Lee I, Young Kang J, Nyol Paik C, Kyung Cho Y, Woo Kim S, Choi MG, Chung IS. Acute esophageal and gastric injury: complication of Lugol's solution. *Scand J Gastroenterol* 2007; **42**: 135-137 [PMID: 17190773 DOI: 10.1080/00365520600825141]
 - 18 **Kanzaki H**, Takenaka R, Kawahara Y, Kawai D, Obayashi Y, Baba Y, Sakae H, Gotoda T, Kono Y, Miura K, Iwamura M, Kawano S, Tanaka T, Okada H. Linked color imaging (LCI), a novel image-enhanced endoscopy technology, emphasizes the color of early gastric cancer. *Endosc Int Open* 2017; **5**: E1005-E1013 [PMID: 29159276 DOI: 10.1055/s-0043-117881]
 - 19 **Khurelbaatar T**, Miura Y, Osawa H, Nomoto Y, Tokoro S, Tsunoda M, Sekiguchi H, Kobayashi T, Funayama Y, Nagayama M, Takezawa T, Mieno M, Ueno T, Fukuda H, Iwashita C, Takahashi H, Ino Y, Kawai A, Yamamoto H. Usefulness of linked color imaging for the detection of obscure early gastric cancer: Multivariate analysis of 508 lesions. *Dig Endosc* 2022; **34**: 1012-1020 [PMID: 34942042 DOI: 10.1111/den.14221]
 - 20 **Ono S**, Kawada K, Dohi O, Kitamura S, Koike T, Hori S, Kanzaki H, Murao T, Yagi N, Sasaki F, Hashiguchi K, Oka S, Katada K, Shimoda R, Mizukami K, Suehiro M, Takeuchi T, Katsuki S, Tsuda M, Naito Y, Kawano T, Haruma K, Ishikawa H, Mori K, Kato M; LCI-FIND Trial Group. Linked Color Imaging Focused on Neoplasm Detection in the Upper Gastrointestinal Tract : A Randomized Trial. *Ann Intern Med* 2021; **174**: 18-24 [PMID: 33076693 DOI: 10.7326/M19-2561]
 - 21 **Kobayashi K**, Miyahara R, Funasaka K, Furukawa K, Sawada T, Maeda K, Yamamura T, Ishikawa T, Ohno E, Nakamura M, Kawashima H, Nakaguro M, Okumura Y, Hirooka Y, Fujishiro M. Color information from linked color imaging is associated with invasion depth and vascular diameter in superficial esophageal squamous cell carcinoma. *Dig Endosc* 2020; **32**: 65-73 [PMID: 31220372 DOI: 10.1111/den.13469]
 - 22 **Nakamura K**, Urabe Y, Oka S, Nagasaki N, Yorita N, Hata K, Masuda K, Kurihara M, Kotachi T, Boda T, Tanaka S, Chayama K. Usefulness of linked color imaging in the early detection of superficial esophageal squamous cell carcinomas. *Esophagus* 2021; **18**: 118-124 [PMID: 32447591 DOI: 10.1007/s10388-020-00749-2]
 - 23 **de Groof AJ**, Fockens KN, Struyvenberg MR, Pouw RE, Weusten BLAM, Schoon EJ, Mostafavi N, Bisschops R, Curvers WL, Bergman JJ. Blue-light imaging and linked-color imaging improve visualization of Barrett's neoplasia by nonexpert endoscopists. *Gastrointest Endosc* 2020; **91**: 1050-1057 [PMID: 31904377 DOI: 10.1016/j.gie.2019.12.037]
 - 24 **Diao W**, Huang X, Shen L, Zeng Z. Diagnostic ability of blue laser imaging combined with magnifying endoscopy for early esophageal cancer. *Dig Liver Dis* 2018; **50**: 1035-1040 [PMID: 29685806 DOI: 10.1016/j.dld.2018.03.027]
 - 25 **Yi N**, Huang P, Zhang W, Jiang C, Liang L. [A comparative study of endoscopic linked color imaging and iodine staining in the diagnosis of multiple primary esophageal carcinoma]. *Chin J Clin Gastroenterol* 2019; **31**: 139-144
 - 26 **Wei WQ**, Chen ZF, He YT, Feng H, Hou J, Lin DM, Li XQ, Guo CL, Li SS, Wang GQ, Dong ZW, Abnet CC, Qiao YL. Long-Term Follow-Up of a Community Assignment, One-Time Endoscopic Screening Study of Esophageal Cancer in China. *J Clin Oncol* 2015; **33**: 1951-1957 [PMID: 25940715 DOI: 10.1200/JCO.2014.58.0423]
 - 27 **Zhang N**, Li Y, Chang X, Lei F, Ma H, Liu J, Yang J, Su M, Sun X, Zhao D, Sun Q, Wei W, Wang G, Wang J. Long-term effectiveness of one-time endoscopic screening for esophageal cancer: A community-based study in rural China. *Cancer* 2020; **126**: 4511-4520 [PMID: 33460056 DOI: 10.1002/cncr.33119]

- 28 **National Quality Control Center of Digestive Endoscopy NCRCfDDS**, National Early Gastrointestinal-Cancer Prevention & Treatment Center Alliance (GECA); Digestive Endoscopy Professional Committee of Chinese Endoscopist Association, Chinese Society of Digestive Endoscopy, Chinese Society of Health Management; Cancer Endoscopy Professional Committee of China Anti-Cancer. [China experts consensus on the protocol of early esophageal cancer and pre-cancerous lesion screening (2019, Xinxian)]. *Chin J Dig Endosc* 2019; **36**: 793-801
- 29 **Jin D**, Wang J, Zhan Q, Huang K, Wang H, Zhang G, Xu Y, Yao J, Sun R, Huang Q, Ye F. The safety and efficacy of 2% vitamin C solution spray for relief of mucosal irritation caused by Lugol chromoendoscopy: a multicenter, randomized, double-blind, parallel trial. *Gastrointest Endosc* 2020; **92**: 554-564 [PMID: [31783028](#) DOI: [10.1016/j.gie.2019.11.028](#)]
- 30 The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; **58**: S3-43 [PMID: [14652541](#) DOI: [10.1016/s0016-5107\(03\)02159-x](#)]
- 31 **Schlemper RJ**, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, Dixon MF, Fenoglio-Preiser CM, Fléjou JF, Geboes K, Hattori T, Hirota T, Itabashi M, Iwafuchi M, Iwashita A, Kim YI, Kirchner T, Klimpfinger M, Koike M, Lauwers GY, Lewin KJ, Oberhuber G, Offner F, Price AB, Rubio CA, Shimizu M, Shimoda T, Sipponen P, Solcia E, Stolte M, Watanabe H, Yamabe H. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000; **47**: 251-255 [PMID: [10896917](#) DOI: [10.1136/gut.47.2.251](#)]
- 32 **Yokoyama A**, Ohmori T, Makuuchi H, Maruyama K, Okuyama K, Takahashi H, Yokoyama T, Yoshino K, Hayashida M, Ishii H. Successful screening for early esophageal cancer in alcoholics using endoscopy and mucosa iodine staining. *Cancer* 1995; **76**: 928-934 [PMID: [8625217](#) DOI: [10.1002/1097-0142\(19950915\)76:6<928::aid-cnrcr2820760604>3.0.co;2-5](#)]
- 33 **Liu M**, Zhou R, Guo C, Xu R, Liu A, Yang H, Li F, Duan L, Shen L, Wu Q, Liu Z, Liu F, Liu Y, Pan Y, Cai H, Weiss NS, He Z, Ke Y. Size of Lugol-unstained lesions as a predictor for risk of progression in premalignant lesions of the esophagus. *Gastrointest Endosc* 2021; **93**: 1065-1073.e3 [PMID: [32950597](#) DOI: [10.1016/j.gie.2020.09.020](#)]
- 34 **Kuehni RG**. Color-tolerance data and the tentative CIE 1976 L a b formula. *J Opt Soc Am* 1976; **66**: 497-500 [PMID: [932844](#) DOI: [10.1364/josa.66.000497](#)]
- 35 **Tsunoda M**, Miura Y, Osawa H, Khurelbaatar T, Sakaguchi M, Fukuda H, Lefor AK, Yamamoto H. New Diagnostic Approach for Esophageal Squamous Cell Neoplasms Using Linked Color Imaging and Blue Laser Imaging Combined with Iodine Staining. *Clin Endosc* 2019; **52**: 497-501 [PMID: [31499608](#) DOI: [10.5946/ce.2018.195](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

