

# Application of linked color imaging in the diagnosis of early gastrointestinal neoplasms and precancerous lesions: a review

Shanshan Wang , Lei Shen and Hesheng Luo

## Abstract

**Introduction:** Minimally invasive endoscopic resection is often effective in the management of early gastrointestinal tumors. However, advanced and more effective methods of endoscopic examination are required to improve the rate of diagnosing early gastrointestinal tumors.

**Discussion:** The development of dye-based image-enhanced endoscopy (d-IEE) and equipment-based image-enhanced endoscopy (e-IEE) has helped improve the diagnostic rate of early gastrointestinal tumor using endoscopy. In some special cases, these methods are still not accurate in diagnosing lesions. On the basis of these e-IEEs, a new endoscopic technique, linked color imaging (LCI), that combines a specific short wavelength narrow band of light with white light, has been developed.

**Conclusion:** In this article, we summarized the characteristics of LCI and the development of research regarding digestive tract examination.

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## Plain language summary

### Application of linked color imaging in early gastrointestinal neoplasms

At present, the complete diagnosis of early gastrointestinal tumors and precancerous lesions can be made by gastrointestinal endoscopy. With the improvement of therapeutic instruments and operators' experience, endoscopic therapy can often achieve significant effect in the treatment of early gastrointestinal tumors. The development and spread of equipment-based image-enhanced endoscopy (e-IEE) mode has helped improve the diagnosis rate of early gastrointestinal tumors under endoscopy. However, in some special cases, these methods are still not accurate for the diagnosis of lesions. On the basis of these E-IEEs, a new endoscopic technique, linked color imaging (LCI), has been developed, which combines a specific short wavelength narrow band of light with white light. LCI can significantly improve the diagnostic rate of all types of gastrointestinal mucosal lesions. Tumor lesions and inflammatory lesions can be distinguished by observing the mucosal microvascular structure and color difference. LCI helps detect early gastrointestinal mucosal lesions by taking advantage of the differences in light absorption of different wavelengths and contrast of enhanced colors in the later stage.

Correspondence to:

**Lei Shen**  
Department of  
Gastroenterology, Renmin  
Hospital of Wuhan  
University, Hubei Zhang  
Road (Formerly Ziyang  
Road), Wuchang District  
No. 99, Jiefang Road 238,  
Wuhan, Hubei Province  
430060, China  
[szggyx2017@163.com](mailto:szggyx2017@163.com)

**Shanshan Wang**  
Department of  
Gastroenterology, Renmin  
Hospital of Wuhan  
University, Wuhan, Hubei  
Province, China

Key Laboratory of Hubei  
Province for Digestive  
System Disease, Renmin  
Hospital of Wuhan  
University, Wuhan, Hubei  
Province, China

**Hesheng Luo**  
Department of  
Gastroenterology, Renmin  
Hospital of Wuhan  
University, Wuhan, Hubei  
Province, China

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## Introduction

Currently, endoscopic resection has been one of methods for the treatment of digestive tract tumors. Minimally invasive treatment methods have been developed, such as endoscopic mucosal resection (EMR) and endoscopic mucosal dissection (ESD). With the improvements in therapeutic instruments and operators' experience, endoscopic therapy can be very effective in the treatment of early gastrointestinal tumors. Furthermore, methods that will improve the diagnostic rate of early gastrointestinal tumors are required to achieve earlier detection and treatment.

To improve further the detection rate of early gastrointestinal tumors using endoscopy, dye-based image enhanced endoscopy (d-IEE) was first developed. For example, indigo carmine staining was used to enhance the irregularity of the mucosa using dyes to identify lesions.<sup>1</sup> In recent years, the development and increasing use of equipment-based image-enhanced endoscopy (e-IEE), including narrow band imaging (NBI), blue laser imaging (BLI), and Fujinon intelligent chromoendoscopy (FICE), has significantly improved the diagnostic rate of early gastrointestinal tumors using endoscopy.<sup>2-4</sup> NBI and BLI utilize changes in the microstructure to identify lesions. BLI-bright is an advanced version of standard BLI, which provides images of more obvious and accurate mucosal and vascular structures.<sup>5</sup> These patterns are also helpful in finding lesions in the gastrointestinal tract. FICE can be used to detect tumors early, but it cannot fully reveal the details of mucosal structure and blood vessels when light intensity is insufficient. In addition to e-IEEs, a new endoscopic technique, linked color imaging (LCI), has been developed; this technique combines a specific short wavelength narrow band of light with white light.

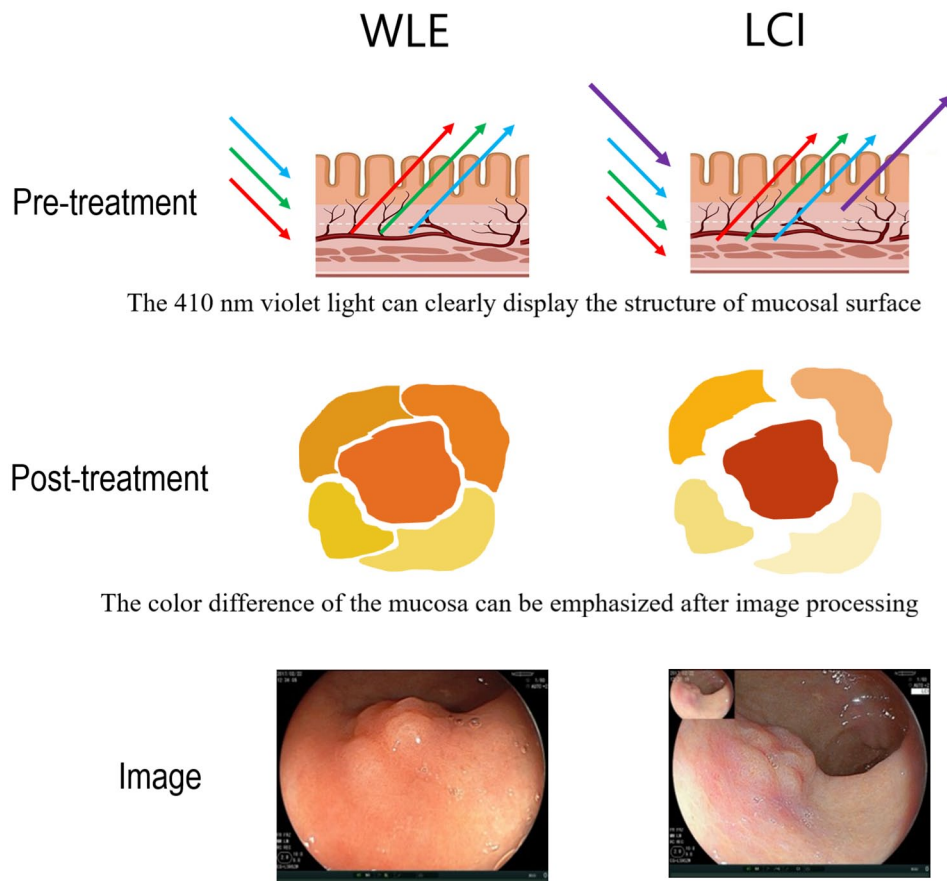
## Characteristics of LCI

Fuji developed the LCI technology in 2014. LCI uses both narrow-band radiation pre-processing and post-processing color technology to classify incoming colors into red, green, and blue. The observed chromatic aberration is increased by redistributing and adjusting the separate colors.<sup>6</sup> A combination of pre-treatment and post-treatment can be used to enhance the color contrast between the neoplastic lesions and the surrounding normal mucosa.<sup>7</sup> The 410 nm violet light can clearly display the surface microstructure and

microvascular system; therefore, LCI can clearly display the structure of blood vessels and the mucosa without amplification. When NBI and BLI are used to observe lesions at a distance, the light in the visual field is too dark to observe the superficial lesions clearly. With novel processing techniques, LCI can still provide sufficient light intensity and bright imaging at a long distance. The wavelength and brightness of the light source of LCI are similar to those of BLI-bright, but the way the host processes it is different. Through image processing, the subtle differences in the red color of the mucosa are emphasized, as well as the differences in hue between the enhanced chroma and the red mucosa color, making the red areas of the mucosa redder and the white areas whiter.<sup>8</sup> By enhancing the color differences in the images, LCI enables the observation of lesions at a distance. LCI distinguishes neoplastic and inflammatory lesions by observing the mucosal microvascular structure and color difference. It can also significantly improve the diagnostic rate of various gastrointestinal mucosal lesions. LCI helps to detect early gastrointestinal mucosal lesions by taking advantage of the differences in light absorption of different wavelengths and enhanced color contrast in the later stage. In addition, this mode can be switched directly on the endoscopic operating system, thereby eliminating the step of spraying dye.

## Color research of LCI

The images under LCI observation are very similar to those seen under white light endoscopy (WLE), while the images provided by NBI and BLI are completely different from those seen using WLE. In fact, compared to WLE, LCI can display clearer images of the vascular morphology of the gastrointestinal mucosa with stronger light intensity, and enhanced color pattern. LCI images are formed by emitting white light and narrow-band short wave light and then post-processing the image to show the well-separated red region. LCI increases the color contrast through image processing, and this can cause the red areas of the mucosa to appear redder and the white areas of the mucosa to appear whiter (Figure 1). The relationship between tumor lesions and microvascular structure has been widely studied.<sup>9</sup> Tumors have irregular vascular structure and microvascular dilation; therefore, there are concentrated dilated capillaries on the superficial surface of the



**Figure 1.** Linked color imaging (LCI) technology application principle.

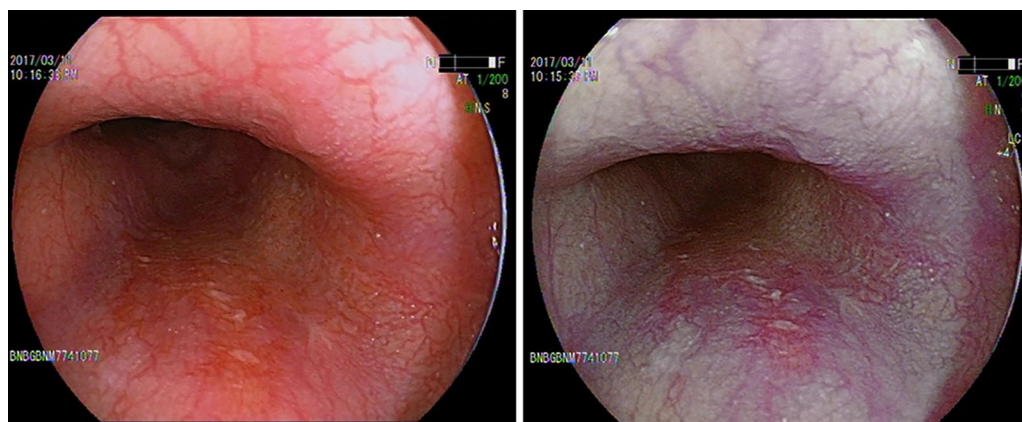
mucosa of tumors. Inflammatory lesions have dilated capillaries in the deep mucosa. In neoplastic lesions, hemoglobin in the superficial capillaries of the mucosa can absorb purple light with a wavelength of 410 nm, but purple light cannot be observed using endoscopy. The final appearance of neoplastic lesions using LCI is orange. In inflammatory lesions, purple light with a wavelength of 410 nm cannot reach deeper capillaries and is directly reflected from the mucosal surface; hence, inflammatory lesions under LCI appear purple in color. In the post-treatment of LCI, the abnormalities of the microvessels and the microstructure of the mucosal surface can be observed in more detail by enhancing the color difference.<sup>10</sup> As the color changes of the lesion precede the morphological changes of the mucosa, LCI can detect abnormal color contrast between the lesion and the surrounding mucosa at an early and more sensitive stage. Thus, LCI can detect inflammatory lesions and precancerous lesions in all types of mucosa at early stages.

## Esophagus

### *Clinical application of LCI in esophageal diseases*

The increased frequency of gastroesophageal reflux disease (GERD) has led to an increase in the incidence of Barrett's esophagus and esophageal adenocarcinoma. LCI, compared to WLE, has led to better visibility for reflux esophagitis (RE) (Figure 2). RE images having better contrast with the surrounding esophageal mucosa and were more clearly viewed with LCI.<sup>11</sup> Non-erosive reflux disease (NERD) includes minimal change esophagitis and shows no endoscopic abnormalities. However, for most endoscopists, it is difficult to detect NERD with conventional WLE. Minimal changes are more easily recognizable using LCI, as the white areas appear whiter and the red areas appeared redder.<sup>12,13</sup>

Barrett's esophagus is a risk factor for esophageal adenocarcinoma. As the incidence of GERD has



**Figure 2.** Linked color imaging (LCI) versus white light endoscopy (WLE) in reflux esophagitis.

increased, the incidence of Barrett's esophagus and esophageal adenocarcinoma has also increased. It is of great significance to improve the diagnostic accuracy of endoscopic techniques in detecting Barrett's esophagus. Current studies have compared the characteristics of WLE, LCI, and BLI in detecting Barrett's esophagus. It was found that under the LCI endoscopic mode the red and purple signs of Barrett's esophagus were significantly enhanced, and pale blood vessels in the esophagus could be clearly detected.<sup>14</sup> LCI also improves the visibility of the short segment of Barrett's esophagus. The images collected from the observation of Barrett's esophagus using LCI showed a high color difference between the areas of Barrett's esophagus and the normal mucosa. The study suggested that early esophageal carcinomas in the LCI model showed obvious red or purplish-red areas, and these were significantly contrasted with the surrounding normal mucosa and showed a clear red-white boundary. This difference is useful and effective in the diagnosis of early esophageal cancer whether combined with magnification endoscopy or not.<sup>15</sup>

#### *Clinical application of LCI in determining the infiltration depth of esophageal carcinoma*

The prognosis of advanced esophageal cancer is generally poor; however, early esophageal cancer can be cured using endoscopic therapy and surgery. The prognosis of esophageal cancer depends on the level of lymph node metastasis and the depth of invasion. Accurate diagnosis of the depth of lesion invasion is an important indicator that can be used to determine the prognosis of esophageal cancer.<sup>16</sup> The infiltration depth of esophageal cancer can be determined using endoscopy, endoscopic

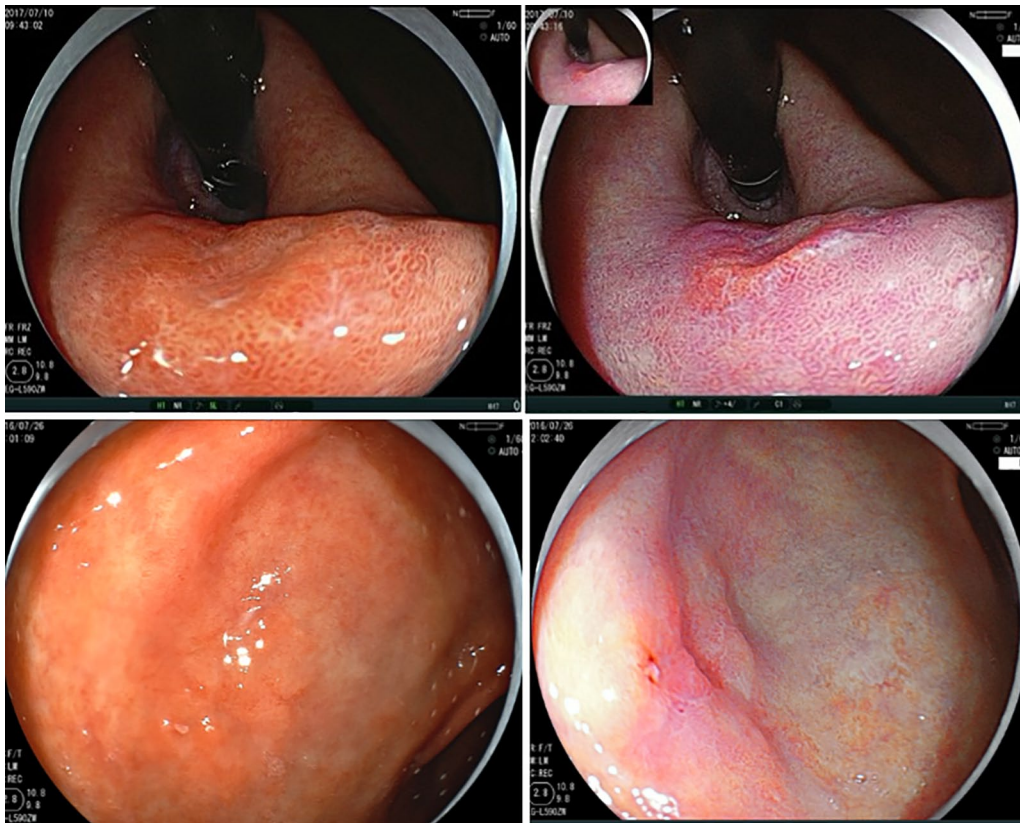
ultrasonography, and esophageal angiography.<sup>16</sup> NBI and BLI have been used to determine the depth of esophageal cancer invasion; however, their diagnostic accuracy is about 57–60% for MM/SM1 (Mucosal muscle/Submucosa) lesions. This accuracy can be further improved.<sup>17–19</sup> The diagnosis of the invasion depth of lesions using WLE is usually based not only on color but also on the morphological characteristics and thickness of lesions, and this requires endoscopic physicians to have certain experience and techniques. However, LCI can only use tonal difference to predict the depth of infiltration, and previous studies have found a correlation between the color difference of the mucosa of esophageal squamous cell carcinoma and the depth of infiltration.<sup>20</sup> For endoscopists that are faced with an unclear diagnosis of early esophageal cancer, LCI can be used as an effective auxiliary diagnostic method.

## **Stomach**

### *Detection of early gastric cancer*

The detection rate of WLE for early gastric cancer is low. Due to the relatively large volume of gastric cavity, NBI and BLI cannot achieve sufficient illumination intensity, so these e-IEE modes are still not ideal for the detection of early gastric cancer. However, LCI has sufficient light intensity to identify early neoplastic lesions on the gastric mucosa. The microvascular system in the superficial mucosa of early gastric cancer lesions can absorb purple light, and the appearance of early gastric cancer is orange red when observed with LCI. Furthermore, LCI can clearly show the difference between early gastric cancer (orange red) and peripheral intestinal metaplasia (purple),





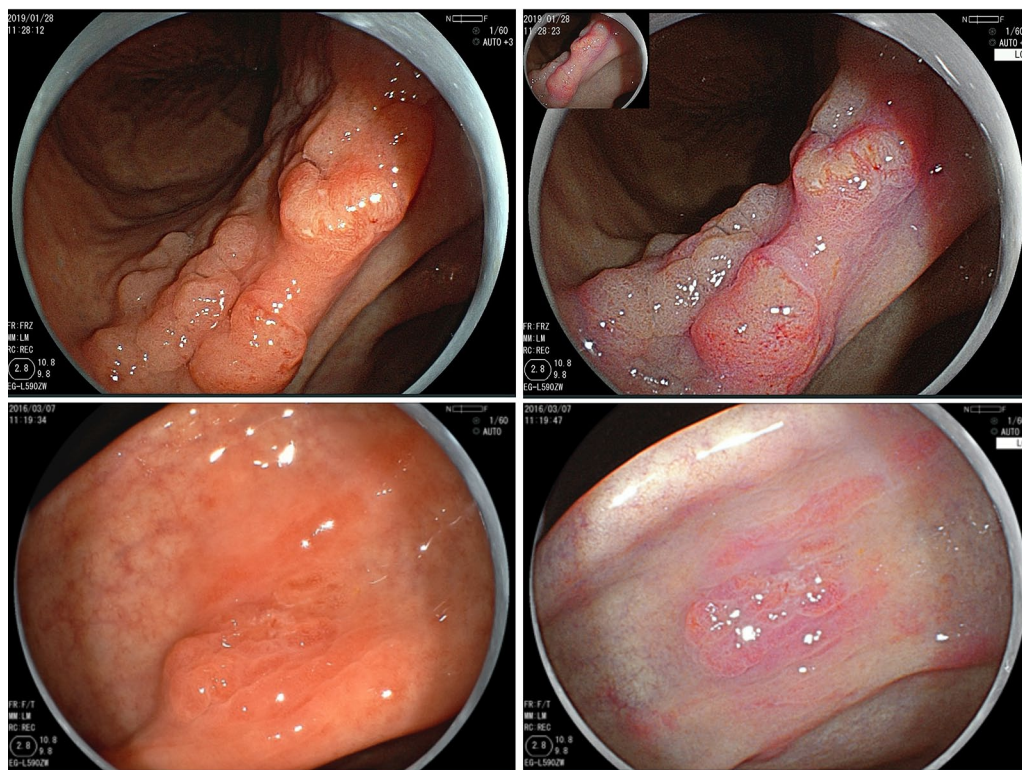
**Figure 3.** Linked color imaging (LCI) versus white light endoscopy (WLE) in early gastric cancer.

which is difficult to detect under white light endoscopic observation.<sup>21</sup> Compared with other e-IEE techniques, such as BLI-bright, LCI has a higher detection rate of early gastric cancer regardless of the level of experience of the endoscopists.<sup>22</sup> Previously, endoscopists mostly distinguished early gastric cancer through morphological differences. LCI technology provides a new method, which is to use color difference to distinguish gastric cancer. The color difference between the disaffected mucosa and the surrounding mucosa in LCI observation images was significantly greater than that of WLE. The chromatic aberration of LCI was about twice that of WLE.<sup>23</sup> By improving the color contrast of LCI, endoscopists can easily distinguish the disaffected mucosa from the normal mucosa, and this greatly promotes the detection of early gastric cancer (Figure 3).

#### Detection of early gastric cancer after *Helicobacter pylori* eradication

LCI can evaluate *H. pylori* infection by the observation of erythema of the gastric mucosa.<sup>24</sup>

Current studies have confirmed that *H. pylori* eradication can prevent the occurrence of gastric cancer, but gastric cancer can still occur after *H. pylori* eradication.<sup>25</sup> Compared to gastric cancer without *H. pylori* eradication, early gastric cancer after eradication has a gastritis-like appearance and is often covered by non-neoplastic epithelium, and this makes the boundary between malignant areas and the normal mucosa unclear.<sup>26</sup> This requires endoscopic physicians to be more observant; however, it is still difficult to identify such lesions clearly even with e-IEE magnifying endoscopy. Studies have reported that early gastric cancer after *H. pylori* eradication appears as an orange mucosa when observed with LCI, while it appears as purple when observed from a distance.<sup>14</sup> When observed with LCI, the difference between neoplastic lesions and the surrounding mucosa can be distinguished even in cases that are observed from a distance.<sup>7</sup> LCI can be used to assess the entire range of the lesion using color differences between the neoplastic lesion and the surrounding mucosa, even without magnification.



**Figure 4.** Linked color imaging (LCI) versus white light endoscopy (WLE) gastric intestinal metaplasia.

#### *Detection of gastric intestinal metaplasia*

Gastric intestinal metaplasia (GIM) is an independent risk factor for gastric cancer. Patients with GIM have a six-fold risk of developing cancer compared to patients without GIM.<sup>27</sup> Therefore, the initial identification of GIM lesions with endoscopy has diagnostic significance. As GIM usually originates on flat mucosa and results in few morphological changes, the ability of WLE to detect it is limited. Compared to WLE, LCI provides more data on changes in the mucosal surface color (Figure 4). Many studies have confirmed that by observing ‘PLC’ (patchy lavender color with a regular mucosal pattern and a clear border), ‘PIM’ (purple in mist; purple mixed with white on the epithelium with signs of mist detected by the non-magnifying LCI observation), or ‘LCS’ (a lavender color sign), along with other signs through LCI, the detection rate of GIM is significantly increased.<sup>28,29</sup>

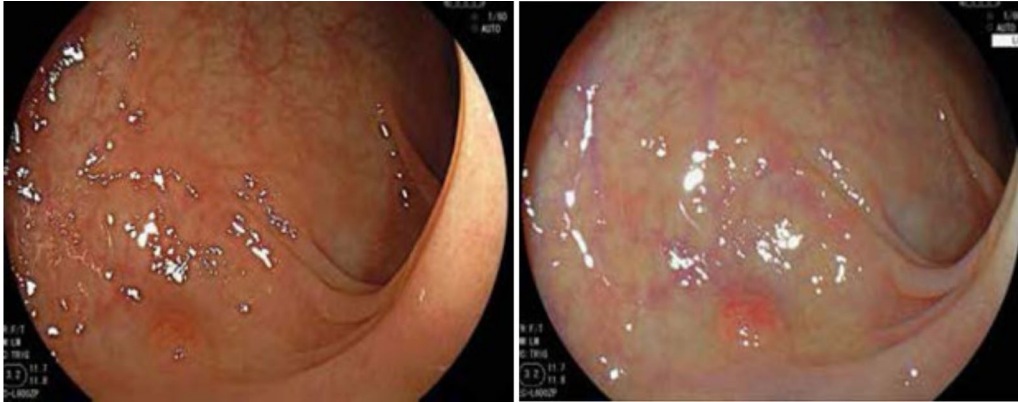
#### **Colon**

##### *Adenoma detection rate and LCI*

The adenoma detection rate (ADR) is a quality indicator of colonoscopy and is also related to the

experience of the endoscopist.<sup>30</sup> Improving ADR can improve the long-term survival of patients with colon cancer by ensuring high quality colonoscopy. Endoscopists have also been improving ADR through improved examination techniques and special equipment. e-IEE techniques, such as NBI, BLI, and FICE are expected to improve ADR. However, due to the lack of sufficient illumination intensity, good observation results cannot be obtained when lesions are observed from a distance. The post-treatment of LCI makes a more obvious color contrast between the neoplastic mucosa and the normal mucosa. Therefore, early lesions, such as flat colorectal adenoma, can be easily detected even without the use of magnification endoscopy. The color difference between the colonic lesion and the surrounding normal mucosa is a key factor in improving ADR during colonoscopy. The detection of colonic lesions also requires sufficient illumination intensity, so the detection rate of NBI and BLI for flat lesions in the colon is not good enough. The color and transparency of the residual fluid in the lumen may also affect the appearance of the lesions at the bottom of the fluid. When observed with NBI or BLI, the color of the residual fluid changes from yellow to deep red, and this significantly





**Figure 5.** Linked color imaging (LCI) *versus* white light endoscopy (WLE) in colonic polyps.

affects the appearance of the lesion. The appearance of such lesions using LCI is similar to those seen when viewed with WLE (Figure 5).

However, the residual fluid is still light yellow in the field of vision, and this has little effect on the appearance of lesions.<sup>31</sup> Similar to gastric lumen observation, LCI can provide sufficient illumination intensity and color enhancement function in the wide intestinal lumen, thus improving the detection rate of colonic lesions.

#### *Detection of sessile serrated adenoma/polyp*

Recent studies have shown that serrated polyps include proliferative polyps and sessile serrated adenoma/polyp (SSA/P) in the right colon. Serrated polyps are considered to be the early state of interphase carcinoma and have a higher risk of carcinogenesis compared to conventional adenomas.<sup>32,33</sup> Studies have also found that the use of LCI can effectively detect such lesions. SSA/P lesions are mostly white, and LCI enhances their visibility by enhancing the whiteness, and this makes the lesions look whiter.<sup>34</sup> Furthermore, the red blood vessels in the background will become redder. The blood vessels in the mucosa will also be interrupted, and this further improves the recognition rate of the lesions. Serrated polyps in the right colon are often overlooked during examination because they resemble the surrounding mucosa in color and are mostly sessile or flat. LCI enhances the color difference between sessile polyps and the surrounding mucosa even when viewed from a distance. As the use of LCI can enhance the vascular morphological differences in the colonic mucosa, the appearance of the vascular

morphology is a key finding in the detection of SSA/P. The large space of the right colon is also a reason for the instances of missed diagnosis of lesions; however, the use of transparent caps can aid in the detection of lesions.<sup>35</sup> The combination of LCI and transparent caps can reduce the incidence of interphase cancer due to missed diagnosis of colonic lesions.

#### *Detection of inflammatory bowel disease*

Endoscopy plays an important role in the diagnosis and treatment of patients with inflammatory bowel disease (IBD) because it can assess the diagnosis and activity of the disease.<sup>36</sup> The current treatment strategy for ulcerative colitis (UC) patients aims to achieve mucosal healing, and the degree of mucosal healing is assessed and graded by a number of endoscopic indicators, including Mayo endoscopic score (MES) and ulcerative colitis endoscopic index of severity (UCEIS). However, many studies have shown that not only achieving mucosal healing, but also further achieving the goal of histological remission may lead to better treatment and prognosis.<sup>37</sup> Due to the existence of multiple histological scoring systems and the inconsistency between WLE and histopathology, the evaluation of disease activity in clinical practice is more complicated.<sup>38</sup> LCI provides an extended range of colors, making red and white colors appear sharper. In particular, for some colonic mucosal redness that is not recognized by the WLE, LCI is able to identify these abnormalities. Studies using LCI in patients with UC have shown that endoscopic LCI assessment is closely associated with Mats histopathological grade.<sup>39</sup> Recent studies have shown that LCI

assessment can accurately predict the recurrence of UC in patients with clinical remission and MES of 0,<sup>40</sup> and can better reflect the prognosis of patients than MES grading.<sup>41</sup> As a new method that can define endoscopic mucosal healing, LCI is a promising tool for predicting the clinical recurrence of UC.

#### *Using LCI to determine the pathological types of colonic lesions*

Classification of colonic pit-pattern openings in the colonic mucosa is of great significance and clinical practical value during the determination of neoplastic and non-neoplastic lesions.<sup>42</sup> LCI combined with chemical staining techniques can obtain accurate pit-pattern typing information. Previous studies have shown that LCI combined with crystal violet staining in magnifying endoscopic mode can even obtain images similar to histopathological evaluations; thus, it significantly improves the ability of endoscopists to judge the depth of colonic lesions.<sup>10</sup> LCI combined with staining is expected to improve the accuracy of the diagnosis of early colorectal tumor invasion depth.<sup>10</sup>

#### *Artificial intelligence and LCI*

With the progress in computer technology, artificial intelligence (AI) technology has been applied more widely in medicine. AI technology with image-enhanced endoscopy is an advanced, new topic in the field of gastroenterological endoscopy and has gradually become a useful image diagnostic tool. Some studies have reported the effectiveness of WLI combined with deep learning in the diagnosis of *H. pylori* infection.<sup>43,44</sup> In recent research, an innovative image diagnosing system using AI and e-IEEs for diagnosing *H. pylori* infection has been generated.<sup>45</sup> This system combined a convolutional neural networks (CNN)-based AI system with BLI and LCI, which showed high accuracy. In another study, investigators used a support vector machine (SVM) as a classification algorithm to construct a machine learning-based algorithm using LCI images to form an automated diagnostic system for *H. pylori* infection that can be evaluated for accuracy by comparing the diagnosis with that of an endoscopist.<sup>46</sup> The computer-aided diagnosis (CAD) system, which was based on LCI combined with deep learning,<sup>47</sup> was observed to have strong diagnostic capability in classifying the *H. pylori* infection of

cases into three categories, to indicate the risk of gastric cancer development, and to prevent accidental retreatment of patients in whom it had been eradicated. The application of the LCI-CAD program in endoscopic inspections may promote the risk stratification of patients and improve the detection of gastric cancer. It is believed that AI technology with LCI is likely to become a useful diagnostic tool for endoscopy in the near future.

#### **Conclusion**

In addition to traditional morphological diagnosis, LCI provides endoscopists with a method of color difference, which can be used to judge lesions based on the histological differences in the superficial mucosa, namely the density and depth of capillaries. However, it is important to note that LCI can only detect observable gastrointestinal mucosal lesions. For some blind spots, such as mucosal folds, LCI cannot improve the observation effect. LCI cannot solve the missed diagnosis rate of all gastrointestinal mucosal lesions; thus, it is necessary to improve the operation training of endoscopists and ensure the examination time. Although the color contrast of LCI mode is relatively strong, it is still unable to judge lesions accurately with unclear boundaries, flat shapes, and the same color as normal mucous. When necessary, the appearance of lesions can be improved by combining LCI with traditional pigment endoscopy.

LCI images are similar to the color-enhanced images of WLE, and this reduces the adaptive process for endoscopists. Compared to other e-IEE techniques, LCI images are easier to operate and have a broad application prospect. With the continuous development of digestive endoscopy, LCI technology has been widely used in clinical practice. It has been used in the detection of *H. pylori* infection, polyps, IBD, early gastrointestinal cancer, and precancerous lesions. Currently, relevant studies locally and internationally continue to refresh our understanding of LCI; furthermore, its effectiveness and accuracy in the diagnosis of gastrointestinal mucosal lesions are widely recognized. However, the clinical application of LCI is still not widespread. We hope that there will be more applications and studies in the future further to standardize and improve the use, methods, and standards of LCI.



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The authors declare that there is no conflict of interest.

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## ORCID iD

Shanshan Wang  <https://orcid.org/0000-0001-7825-8958>

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