Proceedings of Anticancer Research, 2026, Volume 10, Issue 4
http://ojs.bbwpublisher.com/index.php/PAR
Online ISSN: 2208-3553
Print ISSN: 2208-3545

# Research Progress and Evidence-Based Evaluation of Chromoendoscopy in Colonoscopy

**Minhong Zou, Xiaojun Tan*, Yan Li, Ji Wu**

Department of Gastroenterology, Foshan Fosun Chancheng Hospital, Foshan 528000, Guangdong, China

***Author to whom correspondence should be addressed.***



**Abstract:** Colorectal cancer is a high-incidence malignant tumor of the digestive tract worldwide. Colonoscopic screening and complete resection of early lesions serve as the core strategies to reduce its morbidity and mortality. Conventional white-light endoscopy (WLE) exhibits a high missed diagnosis rate for minute adenomas, flat lesions, laterally spreading tumors (LSTs), and inflammatory bowel disease (IBD)-associated dysplasia, which fails to meet the demands of precise early diagnosis. Chromoendoscopy (CE) enhances the fine mucosal microstructure, crypt morphology, and lesion boundaries via topical mucosal spraying of staining agents, thereby significantly improving lesion detection efficacy. Based on evidence-based medical data, this study systematically summarizes the mechanism of action, characteristics of commonly used staining agents, standardized operating procedures, and quality control key points of CE. By integrating randomized controlled trials (RCTs), meta-analyses, and domestic and international authoritative guidelines, this paper hierarchically evaluates its clinical value in adenoma detection, early colorectal cancer diagnosis, LST assessment, IBD-related dysplasia screening, and postoperative follow-up. It further conducts an evidence-based comparison of the diagnostic efficacy among CE, WLE, virtual chromoendoscopy, magnifying endoscopy, and artificial intelligence (AI)-assisted endoscopy. Additionally, the current limitations of existing studies are objectively summarized, and future research directions of this technology are prospected, aiming to provide evidence-based references for the standardized implementation of enhanced colonoscopy and the construction of a stratified early screening strategy for colorectal cancer.

**Keywords:** Chromoendoscopy; Colonoscopy; Colorectal neoplasms; Adenoma detection rate; Evidence-based evaluation; Research progress

**Online publication:** August 11, 2026

## 1. Introduction

According to the 2024 global cancer statistics, new cases and deaths of colorectal cancer consistently rank among the top three of all malignant tumors worldwide, with a rising incidence in young and middle-aged populations year by year, leading to an increasing burden of disease prevention and control [1]. Colonoscopy,

with multiple functions including screening, targeted biopsy, and minimally invasive endoscopic treatment, is regarded as the gold standard for colorectal cancer screening and surveillance [2]. As the primary precancerous lesion of colorectal cancer, adenoma can reduce the canceration risk by more than 70% through early detection and complete resection. However, missed diagnosis remains a prominent problem in clinical practice with WLE: the missed diagnosis rate of minute adenomas (≤ 5 mm in diameter) and flat adenomas in the right colon reaches 20%–30%, and missed lesions constitute the leading cause of interval cancer [3,4]. Therefore, optimizing endoscopic enhancement techniques and improving the visualization of subtle mucosal lesions has become a key research direction in the field of digestive endoscopy.

Chromoendoscopy (CE) has been developed for more than 30 years. It highlights mucosal crypts, orifice structures, and lesion contours through physical contrast or biochemical staining, enabling fine mucosal observation without magnifying equipment, and stands as a traditional enhanced endoscopic technique with sufficient evidence-based support [5]. In recent years, virtual enhancement techniques such as narrow-band imaging (NBI), flexible spectral imaging color enhancement (FICE), and AI-assisted endoscopy have been rapidly popularized. Some clinicians hold the view that CE is cumbersome to operate and tends to be replaced. Nevertheless, multiple meta-analyses and real-world studies have confirmed that CE retains irreplaceable diagnostic advantages in high-risk population screening, IBD surveillance, and detection of depressed early tumors, with the additional strengths of low consumable costs and high accessibility in primary hospitals [6].

From an evidence-based evaluation perspective, this study integrates high-quality clinical studies, systematic reviews, and domestic and international digestive endoscopy guidelines published in the past decade, comprehensively summarizes the basic technical essentials and clinical application evidence of CE, and compares different endoscopic techniques horizontally. Existing shortcomings are analyzed and future research directions are proposed, aiming to provide theoretical support for the standardized application of chromocolonoscopy and the improvement of the stratified screening system for colorectal cancer.

## 2. Basic principles, staining agents, and operational quality control of chromoendoscopy

### 2.1. Diagnostic mechanism

CE improves mucosal imaging through three pathways: physical deposition, epithelial uptake, and chemical reaction, with four core diagnostic advantages. First, contrast enhancement effect. Non-absorbable staining agents only deposit in mucosal grooves and crypt depressions without staining normal flat mucosa, and the light-dark contrast enables rapid identification of flat elevated and minute depressed lesions. Second, visualized pit pattern classification. Staining clearly displays crypt morphology, distinguishing normal, hyperplastic, adenomatous, and cancerous crypts to realize endoscopic “optical biopsy”. Third, accurate lesion boundary delineation. For LSTs and large-area flat adenomas, staining clearly defines lesion margins to guide preoperative planning of endoscopic submucosal dissection (ESD). Fourth, reduced inter-observer variability. Standardized staining objectifies mucosal structure, minimizing missed diagnosis and misjudgment caused by insufficient clinical experience among junior physicians [7].

## 2.2. Evidence-based characteristics of clinically commonly used staining agents

### 2.2.1. Indigo carmine

As the clinically preferred contrast staining agent, indigo carmine is non-absorbable by mucosal epithelium, only depositing in mucosal depressions. It features stable staining, no cytotoxicity, and extremely rare systemic adverse reactions. With a standard concentration of 0.2%–0.4%, it is suitable for total colon screening, preliminary screening of LSTs, and lesion boundary determination, serving as the most promotable staining protocol in primary hospitals [8]. A prospective controlled study conducted by Paiva et al. [9] enrolled 203 participants, who received re-examination via pure WLE and indigo carmine CE, respectively. The results demonstrated that the indigo carmine group had a significantly higher number of newly detected polyps and total polyp detection volume, showing a prominent screening enhancement effect.

### 2.2.2. Methylene blue

Methylene blue is an absorbable staining agent that can be taken up by hyperproliferative intestinal epithelium. Adenomas and early cancers exhibit significantly deeper staining than normal mucosa. It is mostly combined with magnifying endoscopy for precise pit pattern classification, with higher sensitivity for flat minute adenomas than indigo carmine. However, a small amount of the agent can be absorbed into the blood, so cautious use is required in patients with severe renal insufficiency [10]. Currently, the mainstream clinical methylene blue staining methods include topical lesion spraying, submucosal injection, and oral integral staining. Traditional topical spraying is complicated in operation, high in consumable consumption, and time-consuming for endoscopy, resulting in limited clinical application and gradual replacement by submucosal injection staining. In contrast, oral methylene blue staining has been widely applied in the screening and diagnosis of colorectal lesions with the updating of endoscopic techniques, due to its simple operation and stable and objective staining effect.

A large-sample double-blind RCT conducted by Repici et al. [11] further verified the clinical value of this technique. A total of 1205 subjects were enrolled and randomly divided into the oral methylene blue experimental group and the placebo control group at a 1:1 ratio. The results showed that the experimental group yielded significantly higher detection rates of non-polypoid lesions, overall adenomas, and minute adenomas (≤ 5 mm) than the control group (35.07% vs 43.92%, OR=1.66, 95%CI: 1.21–2.26; 47.81% vs 56.29%, OR=1.46, 95%CI: 1.09–1.96; 30.90% vs 37.11%, OR=1.36, 95%CI: 1.01–1.83). These findings confirm that oral methylene blue staining can effectively improve the detection efficacy of various colorectal lesions, especially for minute adenomas that are easily missed in clinical practice.

### 2.2.3. Acetic acid

Acetic acid staining is a commonly used auxiliary technique to improve polyp detection rate in colonoscopy, with the advantages of low cost, convenient access, and simple operation. Recent clinical studies have shown that the combined application of acetic acid staining and NBI endoscopy can further optimize the diagnostic accuracy of colorectal polyps with prominent clinical value. As a reactive temporary staining agent, 1%–3% acetic acid induces transient dehydration and whitening of epithelial cells with temporary highlighting of crypt structures, which fades naturally within 30–60 seconds without flushing, enabling time-efficient outpatient rapid screening. Nevertheless, its short staining duration limits its application in large-scale and long-term lesion evaluation [12]. A prospective single-arm study by Wiessner et al. [13] enrolled 55 patients, who first underwent WLE examination followed by acetic acid combined with NBI re-examination, with a

total of 63 polyps detected. The study showed no significant difference in lesion diagnostic accuracy between the two methods (85.5% vs 80.6%, $P$=0.450). However, the combined mode significantly improved the clarity of lesion boundary display, with a clear boundary visualization rate of 98.4%, which was remarkably higher than 75.8% of pure WLE ($P < 0.001$).

#### 2.2.4. Special staining agents

Crystal violet and eosin are only used for precise classification under high-magnification endoscopy. They provide durable staining but cause slight mucosal irritation, thus rarely applied in routine screening.

## 3. Evidence-based evaluation of clinical applications of chromoendoscopy

### 3.1. Improvement of adenoma detection rate (ADR)

ADR is the core indicator for evaluating colonoscopy screening quality. Multiple meta-analyses involving tens of thousands of subjects published from 2020 to 2022 consistently confirmed that total colon indigo carmine CE increased the overall ADR by 18%–34% compared with pure WLE, with the most prominent enhancement for minute adenomas (≤ 5 mm) and a nearly 40% increase in the detection of flat adenomas in the right colon [14,15].

Stratified population analysis showed that average-risk screening populations obtain moderate diagnostic benefits, while high-risk populations (with a history of adenomas or family history of colorectal cancer) gain significantly higher diagnostic benefits from CE, with a GRADE Ia evidence level. The underlying mechanism is that WLE is prone to missing flat non-protruding adenomas in the right colon, while CE intuitively visualizes subtle mucosal depressed structures and substantially reduces interval cancers caused by missed diagnosis.

### 3.2. Differential diagnosis of early colorectal cancer and intraepithelial neoplasia

Combined magnifying CE enables clear pit pattern classification: type I and II indicate normal/hyperplastic mucosa, type IIIs, IIIL, and IV suggest adenomas, and type V is highly suggestive of intramucosal or submucosal invasive cancer. Systematic review data showed that magnifying CE achieves a sensitivity of 91.2% and a specificity of 88.7% in the diagnosis of high-grade intraepithelial neoplasia and early colorectal cancer, with a Kappa value of 0.82 for consistency with postoperative pathological results, superior to single WLE and pure NBI [16].

For clinically challenging depressed early cancers, which only present with slight mucosal redness and erosion under WLE and are easily misdiagnosed as inflammation, indigo carmine staining clarifies depressed boundaries. Combined with pit pattern analysis, it can rapidly assess invasion depth and guide minimally invasive endoscopic resection or surgical treatment.

### 3.3. Detection and preoperative evaluation of laterally spreading tumors (LSTs)

LSTs grow horizontally along the mucosa with unobvious protrusion and higher malignant transformation potential than ordinary polyps, constituting a high-risk type of missed diagnosis in colonoscopy. A meta-analysis including 12 RCTs revealed that CE increases the LST detection rate by 42% and accurately distinguishes granular and non-granular LSTs. Non-granular LSTs have a higher risk of submucosal invasion; CE clearly identifies subtle marginal depressions of lesions, provides boundary markers for complete ESD dissection, and reduces the risk of postoperative residual lesions and recurrence [17].

### 3.4. Surveillance of inflammatory bowel disease (IBD)-associated dysplasia

Patients with long-term ulcerative colitis and extensive Crohn's disease have an 8–15 times higher risk of colorectal cancer than the general population, and conventional random WLE biopsy misses more than 60% of dysplastic lesions. Guidelines from the European Crohn's and Colitis Organization (ECCO) and the IBD Group of the Chinese Society of Gastroenterology strongly recommend CE-guided targeted biopsy as the standard protocol for long-term IBD surveillance (evidence level Ia).

Evidence-based data indicate that the dysplasia detection rate of CE-guided targeted biopsy is 2.3–4.8 times that of random WLE biopsy. It accurately identifies flat and minute low/high-grade dysplastic mucosal lesions, avoids massive invalid random biopsies, shortens the pathological diagnosis cycle, and reduces the long-term canceration risk [18].

### 3.5. Post-adenoma resection follow-up and surveillance

Regular colonoscopic follow-up is required 3–5 years after complete adenoma resection, with residual minute adenomas and occult recurrent lesions as the key surveillance targets. Prospective cohort studies show that CE for postoperative follow-up increases the recurrent lesion detection rate by 27% compared with WLE. It can identify minute occult adenomas around surgical scars, enable timely intervention, and reduce the risk of interval cancer, making it suitable for high-risk follow-up populations after resection of high-grade adenomas, multiple adenomas, and LSTs.

## 4. Evidence-based comparison of chromoendoscopy with other enhanced endoscopic techniques

### 4.1. Chromoendoscopy vs Conventional White-Light Endoscopy

All published systematic reviews draw consistent conclusions: CE is comprehensively superior to WLE in the detection of adenomas, minute flat lesions, LSTs, and IBD-associated dysplasia, with no contradictory high-quality evidence. As a simple and low-cost technique to improve the diagnostic performance of basic colonoscopy, it is suitable for popularization in hospitals at all levels.

### 4.2. Chromoendoscopy vs Virtual Chromoendoscopy (NBI/FICE)

NBI requires no spraying of a staining agent, with a simpler operation process and higher compliance in routine outpatient screening. However, the two techniques have distinct dominant clinical scenarios. Meta-analyses show that NBI and indigo carmine CE have no statistically significant difference in the diagnosis of ordinary protruding polyps. In contrast, CE presents higher image contrast and diagnostic accuracy for depressed early cancers, minute flat adenomas in the right colon, and IBD-associated mucosal dysplasia ($P < 0.05$) [19].

Health economic evaluation demonstrates that the consumable cost of CE is only 1/20 of the upgrade cost of virtual chromoendoscopy equipment. It delivers significantly higher cost performance in primary medical institutions and large-scale population screening. The two techniques are complementary rather than substitutive.

### 4.3. Combined application of chromoendoscopy and magnifying endoscopy

The combination of magnifying endoscopy and CE is currently the gold standard for pit pattern classification diagnosis. Single CE only observes gross lesion morphology, while combined magnifying endoscopy enables accurate interpretation of mucosal crypt microstructures. This combined technique is applied for the

evaluation of early cancer invasion depth and precise preoperative ESD assessment, serving as an essential technical combination in tertiary hospital digestive endoscopy centers.

### 4.4. Combined application of chromoendoscopy and artificial intelligence-assisted endoscopy

Artificial intelligence can automatically identify and mark suspected intestinal mucosal polyps, while insufficient contrast of conventional white-light images easily leads to missed detection. CE significantly enhances lesion boundaries and texture features, which improves the sensitivity of AI automatic identification and reduces false-negative results when input into AI models. As an emerging research hotspot in recent years, small-sample studies have confirmed that the combined application can further reduce the adenoma missed diagnosis rate.

## 5. Conclusion

With sufficient grade Ia evidence-based medical support, chromoendoscopy features high safety, low consumable cost, and wide accessibility. It can significantly improve the detection rates of minute colorectal adenomas, flat lesions, LSTs, and IBD-associated dysplasia, possessing unique clinical value in the differential diagnosis of early colorectal cancer, preoperative lesion evaluation, and postoperative follow-up surveillance. Compared with virtual chromoendoscopy, CE has prominent diagnostic advantages in detecting depressed lesions and monitoring high-risk populations, and the two techniques can be applied complementarily.

Current limitations of CE include time-consuming operation, insufficient standardized training, and lack of long-term prognostic data. Future research should unify operating specifications, improve the training system for primary physicians, promote research on targeted staining agents, intelligent spraying equipment, and AI-assisted combined diagnosis, and conduct long-term real-world cohort follow-up studies. These efforts will further explore the application value of CE in early screening and diagnosis of colorectal cancer and optimize the stratified prevention and control system for digestive tract tumors in China.

## Funding

Intramural Research Projects of Foshan Greater Bay Area General Hospital (Project No.: FX2025016)

## Disclosure statement

The authors declare no conflict of interest.

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