Advanced Endoscopic Imaging for Detection of Dysplasia in Inflammatory Bowel Disease

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KEYWORDS

• Virtual chromoendoscopy • Dye-spray chromoendoscopy • Dysplasia
• Colorectal cancer • Inflammatory bowel disease

KEY POINTS

- Chronic inflammation predisposes patients with colonic inflammatory bowel disease (IBD) to develop colorectal cancer (CRC).
- Surveillance programs enable early detection of dysplastic lesions and CRC.
- IBD surveillance should be performed in conditions of endoscopic remission and good bowel preparation.
- Both virtual chromoendoscopy and dye-spray chromoendoscopy in conjunction with targeted biopsies are considered acceptable in the hands of experienced endoscopists.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition affecting the gastrointestinal (GI) tract, and affected individuals are at 2.4-fold higher risk of developing colorectal cancer (CRC). To facilitate early detection and treatment of dysplastic lesions, these patients require frequent endoscopic surveillance.[1,2] The risk of CRC generally begins to increase approximately 8 to 10 years after symptom onset and continues to increase linearly over time.[3] Although only 1% to 2% of IBD patients develop CRC in their lifetime, it contributes to 10% to 15% of IBD-related mortality.[4]

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Chronic, longstanding inflammation leading to DNA oxidative stress and genomic instability is considered the main trigger for neoplastic changes and tumor development.[5,6] Other factors associated with the magnitude of additional CRC risk include disease extent, disease duration and severity, or concurrent primary sclerosing cholangitis (PSC). [1,7,8]

The complex background of inflamed mucosa in IBD and the morphologic diversity of the lesions make early detection of neoplasia challenging. CRC in IBD typically follows the inflammation-dysplasia-carcinoma sequence and occurs over a shorter timeframe as compared to sporadic CRC.[5,6] This may account for morphologic variations of IBD-related dysplasia, from subtle, flat lesions that blend into the surrounding mucosa to ulcerating or sessile growths resembling inflammatory changes.[9,10] These temporal and morphologic considerations have historically guided screening surveillance colonoscopy programs that have been developed to mitigate the CRC-associated morbidity and mortality.[3,11,12]

A downward trend in the relative risk of incident CRC and related mortality has been reported, likely relating to more effective control of inflammation with the advent of new and more effective therapies and to refined surveillance strategies.[2] Several studies since have supported the benefit of surveillance programs by reporting a higher rate of CRC detection as well as a lower rate of mortality from CRC, when compared to no surveillance.[13,14] This shift in prevalence has coincided with the introduction of new optical technologies, with improved resolution and the adoption of adjunct surveillance methods such as dye-spray chromoendoscopy (DCE).

Subsequently, the Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations (SCENIC) International Consensus statement published in 2015 recommended the use of high-definition (HD) rather than standard-definition (SD) white-light endoscopy (WLE) and of DCE with targeted biopsies as standard of care. [15]

Corresponding to the evolution from SD to HD and magnification endoscopy (ME), various forms of image-enhanced endoscopy (IEE) have been developed to characterize mucosal and submucosal features. In this review, the authors shall summarize available IEE technologies, including those with a less defined role or currently under research, such as ultra-HD and molecular endoscopic imaging, and discuss their clinical application in detecting IBD-related dysplasia.

IEE can be classified into conventional DCE, based on intraluminal application of physical dyes enhancing different features of mucosal architecture, and equipment-based methods/virtual chromoendoscopy (VCE) techniques.[16] VCE methods include (1) narrow-band imaging (NBI), (2) flexible spectral imaging color enhancement (FICE), (3) blue laser light imaging/linked-color imaging (BLI/LCI) (4) i-SCAN digital contrast (i-SCAN), (5) texture and color enhancement imaging (TXI) (**Table 1**).

Additionally, ultra-HD endoscopy modalities, such as confocal laser endomicroscopy (CLE) and endocytoscopy (EC), enable real-time histologic assessment of colonic mucosa. Molecular imaging techniques include autofluorescence (AFI), based on the properties of light-tissue interaction, and fluorescent molecular endoscopy (FME) which uses labeled molecular probes, such as antibodies, against specific targets in the gastrointestinal tissue. These techniques can be combined with VCE[18] or with ultra-HD modalities such as CLE.[19]

PREREQUISITES FOR DYSPLASIA DETECTION

To perform high-quality surveillance and effective chromoendoscopy, good bowel preparation is imperative. All residual debris and fluid should be washed and cleared.

Table 1
Overview of main randomized controlled trials comparing dysplasia detection rates between dye-based chromoendoscopy and high-definition white-light endoscopy

Year, Study	Study Design	Sample Size	Techniques Compared	Dysplasia Detection Rate, %	Conclusions
Yang et al,[84] 2019	RCT	210	HD-WLE DCE	20.6 12	Inadequately powered to show a significant difference
Alexandersson et al,[17] 2020	RCT	305	HD-WLE DCE	14 6	Higher diagnostic yield for DCE
Wan et al,[83] 2020	RCT	69	HD-WLE HD-DCE	20.4 4.2	CE with targeted biopsies more effective than WLE with targeted biopsies
Iacucci et al, 2018 [37]	RCT	270	HD-WLE HD-VCE HD-DCE	18.9 17.8 11.1	Diagnostic yield was similar between the three groups

Abbreviations: DCE, dye-based chromoendoscopy; HD-WLE, high-definition white-light endoscopy; RCTs, randomized controlled trials; VCE, virtual chromoendoscopy.

During withdrawal, position change improves visualization by helping to expose the mucosa, thus increasing the chance of detecting more lesions. Lesions should be closely examined for variance in color, vascular pattern, and border and further classified according to Paris classification.[20]

In 2022, the European Society of Gastrointestinal Endoscopy (ESGE) and United European Gastroenterology (UEG) have developed key indicators for surveillance colonoscopy in IBD to be applied in 3 clinical settings: clinical suspicion of IBD, endoscopic assessment of disease activity in known IBD patients, and surveillance, with the aim of optimal detection of pre-malignant lesions. These indicators include adequate bowel preparation, adequate photo-documentation of the procedure, the use of HD endoscopy and DCE or VCE, in combination with targeted biopsies, quiescent disease at the time of surveillance, and neoplasia detection rate that should exceed the minimum standard of $\geq$8%.[21,22]

ENDOSCOPIC DETECTION OF DYSPLASIA IN INFLAMMATORY BOWEL DISEASE

Standard-Definition White-Light Endoscopy Versus High-Definition White-Light Endoscopy

Historically, SD-WLE with extensive ($\geq$32) 4-quadrant non-targeted (random) biopsies every 1 to 2 years was the preferred method for CRC prevention in IBD. However, this method provides a limited sampling of the colon surface area (<1%) and the accuracy is low (overall sensitivities for dysplasia and cancer were 61.3 and 76.1, respectively).[23] The introduction of DCE and HD technology has demonstrated a 3.2-fold increase in intraepithelial neoplasia detection compared to random sampling method.[24]

Prior to current generation systems, SD endoscopes generated images of 400K pixels and a 4:3 aspect ratio.[25] This resolution limited the ability to discriminate subtle mucosal alterations often seen with flat dysplastic lesions. HD is an advanced technology employing an HD monitor and high-resolution charged couple-device. These endoscopes produce image signals with resolution of 1 to 2 million pixels and have a wider field of view[26] (170 HD vs 130 SD). Moreover, HD endoscopes may be equipped with a zoom function that allows for up to 150-fold magnification of images without loss of resolution.[27]

HD-colonoscopy ensures a better characterization and definition of the borders of neoplastic lesions in IBD and using an HD system was associated with a 2-fold higher dysplasia detection rate on targeted biopsy when compared to SD-WLE.[25] A randomized controlled trial (RCT) by Iacucci and colleagues comparing i-SCAN VCE or HD-WLE to DCE has not only shown that the former are non-inferior for detection of dysplastic lesions but also that HD-WLE alone was sufficient for detection of all neoplastic lesions.[28]

Image-Enhanced Endoscopy Techniques

IEE is based on improving visualization of mucosal surface patterns and microvasculature of pre-neoplastic and neoplastic lesions by providing high-contrast endoscopic images through dye based or optical and digital technologies.[16,29]

Dye-based chromoendoscopy

DCE is performed by spraying a surface contrast dye (indigo carmine) or an absorbed cellular-staining agent (methylene blue or crystal violet) within the bowel lumen in segments of 20 cm at a time, to enhance mucosal irregularities, lesion borders, surface pit-pattern, or size of suspicious lesions (**Fig. 1**).[30] Indigo carmine seeps into the crevices and grooves between cells, highlighting fine mucosal structures and abnormalities. Methylene blue and crystal violet are absorbed by the mucosal epithelium,

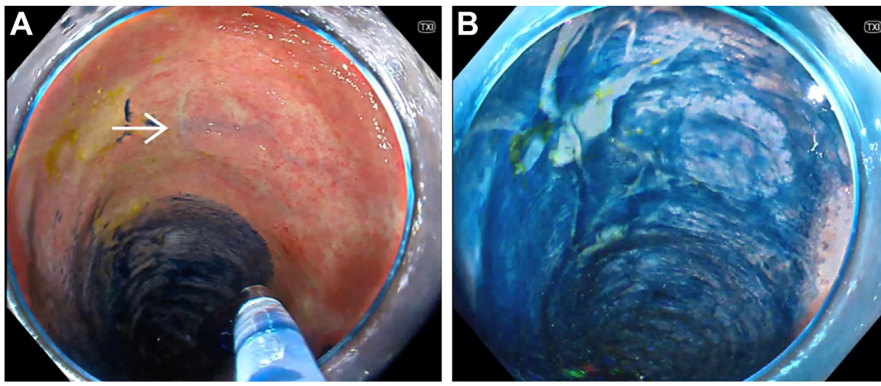

Fig. 1. Sigmoid colon lesion (*white arrow*), Paris 0-IIa, Kudo pit-pattern II in texture and color enhancement imaging (TXI) (*A*) and dye-based chromoendoscopy (*B*) with indigo carmine.

differentiating lesions with inflammation or dysplasia by exhibiting different degrees of stain uptake.[31]

Dye-spray chromoendoscopy versusstandard-definition white-light endoscopy. Data from randomized controlled trials demonstrating superiority of DCE to SD-WLE alone in dysplasia detection led to the recommendation of DCE as the preferred surveillance method by the 2015 SCENIC consensus. [15,25,32,33]

Dye-spray chromoendoscopy versus high-definition white-light endoscopy. The use of DCE with HD-WLE was only conditionally recommended by the SCENIC group15, as HD endoscopes provide higher quality detail and improved tissue discrimination when compared to SD technology. In this context, the value of DCE became a matter of debate. Data had initially been contradictory; a meta-analysis by Feuerstein and colleagues including data from 10 (RCT and non-RCT) studies, concluded that DCE is superior to SD-WLE, but not superior to HD-WLE[24] as reported by non-RCT studies; however, RCT data have shown only a slight benefit of DCE over HD-WLE, with a very low quality of evidence. A further meta-analysis of 17 RCTs totaling almost 2500 patients by Resende and colleagues also reported superiority of DCE vs SD-WLE, but not over HD-WLE.[34] A multicenter, prospective RCT has shown comparable results in dysplasia detection between HD-DCE and HD-WLE (3.9% vs 5.6%), but a subsequent trial reported higher detection yield for HD-DCE versus HD-WLE. [17]

Most recent data from a meta-analysis of 6 RCTs comprising nearly 1000 patients have revealed higher success rates of dysplasia detection with DCE than HD-WLE (18.8% vs 9.4%, respectively).[35] DCE with targeted biopsies should therefore be considered, but due to its cumbersome nature, longer procedure times, and inconsistent availability, its widespread adoption in routine daily practice is limited.[36] The main recent RCTs assessing DCE against HD-WLE for dysplasia detection in IBD are summarized in **Table 1**.

Virtual chromoendoscopy

Following the SCENIC consensus15 guidance, several RCTs have reported similar dysplasia detection rate between VCE and DCE, with the advantage of a shorter examination time in most trials; furthermore, different VCE techniques were used with

similar results.[37–40] The use of VCE with targeted biopsies for dysplasia detection has therefore been adopted by ESGE[41] recent guidelines as alternative to DCE (**Fig. 2**).

VCE includes technologies that highlight mucosal surface and microvasculature through the use of wave-length-specific light or through digital post-processing, in conjunction with HD imaging (**Fig. 3**). VCE includes various systems such as narrow-band imaging (NBI) (Olympus, Tokyo, Japan), flexible spectral image color enhancement (FICE) (Fujifilm, Tokyo, Japan), blue laser light/linked color imaging (BLI/LCI, Fujifilm, Tokyo, Japan), i-Scan digital contrast (Pentax), and texture and color enhancement (TXI, Olympus, Tokyo, Japan).[42] These are "push-of-a-button" techniques, easily available during endoscopic examination. Most relevant RCT data assessing VCE against WLE or DCE are summarized in **Table 2**.

Narrow-band imaging. NBI is the first and most widely used optical image enhancement technology based on wavelength-specific light and the principle of light penetration.[43] An optical filter of the illuminating light reduces the wavelengths of blue (415 nm) and green (540 nm) lights of the WLE spectrum, which are selectively absorbed by hemoglobin. Therefore, the vessels will appear dark and the contrast in the mucosal layer is enhanced. [44] Newer NBI systems introduced in 2020 with EVIS X-1 endoscopes (Olympus, Tokyo, Japan) provide notable improvements such as brighter image quality, expanded depth of field (EDOF), and × 90 magnification power [44] (see **Fig. 3**).

Several RCTs have assessed the performance of NBI for dysplasia detection against WLE (SD or HD) and against DCE (**Table 2**). When compared to SD-WLE, the use of a first generation prototype NBI system did not improve dysplasia detection[45]; this could be attributed to the diminished brightness of the images generated by first generation models. Further studies using a second generation NBI system with improved source of light and HD technology also failed to show superior performance for detection of dysplasia; NBI, however, detected more non-neoplastic lesions than HDE.[46]

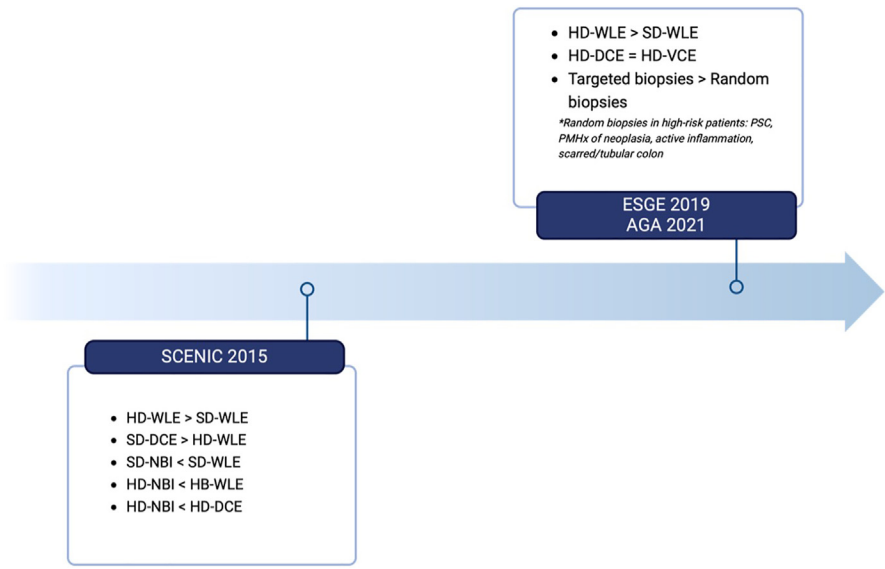

Fig. 2. Evolution of recommendations for endoscopic imaging techniques in inflammatory bowel disease (IBD) surveillance beyond SCENIC consensus. * indicates "Exception", as random biopsies are still necessary in the high risk category.

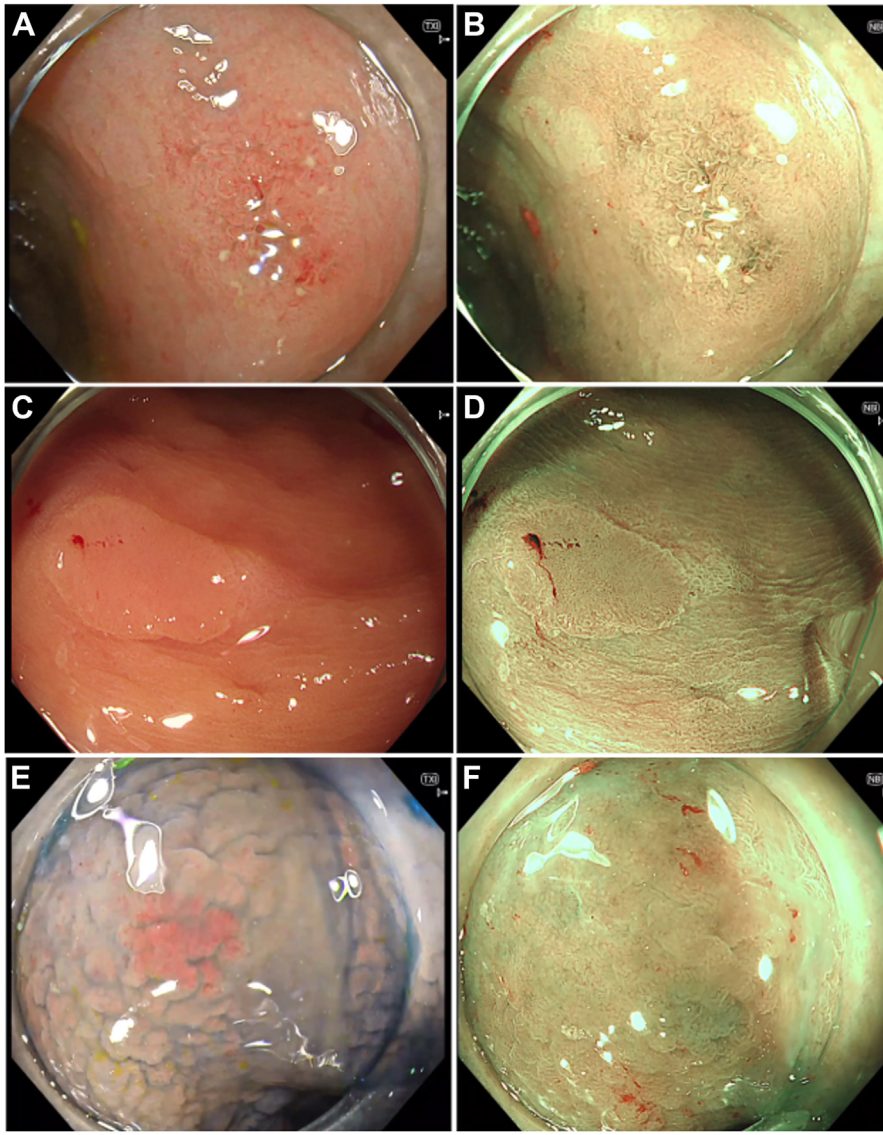

Fig. 3. Flat dysplastic lesions in IBD as assessed by high-definition white-light endoscopy (HD-WLE), TXI and narrow-band imaging (NBI). Paris 0-IIa, JNET 2B in HD-WLE and near-focus (*A*) and NBI and near-focus (*B*); Paris 0-IIa, JNET 2A in HD-WLE and near-focus (*C*) and NBI and near-focus (*D*); Paris 0-IIb JNET 2A, in TXI/DCE (*E*) and NBI (*F*).

The first study to compare NBI with DCE, a single-center crossover trial by Pellise and colleagues, did not find any difference in dysplasia detection rate between the 2 groups[47]; however, a higher miss rate was observed in the NBI group versus the DCE group. Similarly, a further study comparing DCE with NBI found no differences in dysplasia detection rate between groups, although DCE proved more sensitive in detecting lesions for targeted biopsies.[48]

Table 2
Overview of randomized control trials comparing virtual chromoendoscopy with white-light endoscopy (standard-definition or high-definition) or dye-based chromoendoscopy

Year, Study	Study Design	Sample Size	Comparators	Dysplasia Detection Rate, n%
NBI				
Dekker et al,[43] 2007	RCT crossover	42	SD-WLE NBI 1st gen	17.3 23
Van der Broek et al,[44] 2011	RCT crossover	48	HD-WLE NBI 2nd gen	9.2 11
Pellisé et al,[44] 2011	RCT crossover	60	NBI 2nd gen DCE (indigo carmine)	21.5 21.2
Ignjatovic et al,[45] 2012	RCT parallel	220	HD-WLE NBI 2nd gen	9 9
Efthymiou et al,[46] 2013	RCT	44	DCE NBI 2nd gen	15.9 13.8
Leifeld et al,[47] 2015	RCT	159	HD-WLE NBI 2nd gen	48 57
Bisshops et al,[38] 2018	RCT parallel	131	DCE (methylene blue) NBI 3rd gen	21.2 21.5
i-SCAN				
Iacucci et al,[48] 2018	RCT parallel noninferiority	270	HD DCE i-SCAN	25.6 24.4 15.6
Kandiah et al,[49] 2021	RCT parallel	188	HD WLE i-SCAN OE-Mode 2	23.4 14.9
Gonzales-Bernardo et al,41 2021	RCT parallel	129	DCE (indigo carmine) i-SCAN 1	17.9 11.3
FICE				
Gulati et al,[39] 2018	RCT crossover	48	DCE FICE	9.9 8

Abbreviations: DCE, dye-based chromoendoscopy; FICE, flexible spectral imaging color enhancement; HD-WLE, high-definition white-light endoscopy; NBI, narrow-band imaging; RCTs, randomized controlled trials; SD-WLE, standard-definition white-light endoscopy

More recently, a landmark RCT evaluating NBI against DCE by Bisshops and colleagues reported similar performance between the 2 techniques in terms of dysplasia detection: 21.2% for DCE and 21.5% for NBI, respectively.[38]

Real-life data support the findings from clinical trials; a prospective, observational, segmental tandem endoscopic study in 40 patients with ulcerative colitis (UC) reported no difference between HD-NBI and HD-DCE against HD-WLE for dysplasia detection.[50] However, HD-DCE increased the detection rate for sessile serrated lesions/polyps (SSAs/Ps) lesions when compared to HD-NBI and HD-WLE (odds ratio (OR) = 3.16, 95% CI: 0.83–11.92).

i-SCAN. i-SCAN is a software-based digital post-processing filter technology providing HD images using image enhancement functions. Currently, 3 modes are available: iSCAN 1, based on surface enhancement (SE) and contrast enhancement technologies (CE), used for detection; iSCAN 2 combines SE and tone enhancement functions (TE) for better lesion characterization; iSCAN 3 is a combination of all 3

functions (SE, CE, and TE) for lesion detection, characterization, and localization, respectively.[44] The new iSCAN-OE technology is a combination of optical and digital enhancement CE in a single system and involves all 3 algorithms: SE, TE, and optical enhancement.

Three RCTs have evaluated the performance of i-SCAN against HD-WLE and DCE so far. Iacucci and colleagues conducted a non-inferiority parallel RCT on 270 patients, equally randomized to HD-WLE, DCE, or iSCAN OE mode 02. VCE or HD WLE was not inferior to DCE for detection of colonic neoplastic lesions during surveillance colonoscopy. In fact, in this study, HD WLE alone was sufficient for detection of dysplasia, adenocarcinoma, or all neoplastic lesions.[37]

In the (a comparison of high definition white light endoscopy and high definition virtual chromoendoscopy for the detection of intraepithelial neoplasia in longstanding colitis: a randomised control trial [VIRTUOSO]) multicenter trial, 188 patients with long-standing UC or Crohn colitis were randomized 1:1 to undergo surveillance colonoscopy either with VCE (iSCAN OE mode 2) or HD-WLE performing targeted and random biopsies in each arm. No difference was observed in the neoplasia detection (VCE 14.9% vs HD-WLE 24.2%; P5.14) or withdrawal time (25.5 minutes and 24 minutes for VCE and HD-WLE, respectively) between the 2 techniques.[51]

A single center, parallel RCT evaluated the effectiveness of i-SCAN mode 1 against CE with indigo-carmine for colonic neoplastic lesions detection in 129 patients with longstanding IBD; no significant differences were seen between the 2 techniques.[40]

A retrospective case-control study with 191 patients evaluating i-SCAN twin mode 1 to 3 for dysplasia detection against DCE (indigo carmine) reported similar diagnostic performance between the 2 methods.[50]

Flexible spectral imaging color enhancement. Similar to NBI, FICE enhances mucosal and superficial vasculature visualization. FICE utilizes post-processing filters that select a narrow band of wavelengths from white-light endoscopy. Images are reconstructed using a single wavelength and assigned to red, green, or blue inputs to display a combined image. FICE has 10 available filter settings that can be altered by the endoscopist. [42]

Although it can improve the analysis of pit-pattern and of mucosal junction between normal and pathologic tissue, FICE poses difficulties in providing high-contrast images of micro vessels under white light; moreover, choosing the right FICE channel according to the clinical case may prove challenging.[31] These drawbacks led to the development of BLI and LCI.

Data assessing the performance of FICE for dysplasia detection are limited, as most studies are directed toward lesion characterization. A crossover RCT (a comparison of high definition white light endoscopy and high definition virtual chromoendoscopy for the detection of intraepithelial neoplasia in longstanding colitis: a randomised control trial [CONVINCE]) of DCE (indigo carmine) versus VCE with FICE (FICE-8 mode) showed that VCE and DCE performed similarly (diagnostic accuracy of 76.9% and 93.7%, respectively).[39]

Blue laser light imaging. BLI was installed in the LASEREO (laser light source) and ELUXEO (LED light source) endoscopic systems (Fujifilm, Tokyo, Japan) to address FICE's limitation in producing bright and high-contrast images. Both laser and LED BLI use a 410 nm NB wavelength to contrast hemoglobin and visualize high-contrast mucosal superficial vessels and structures.[52] Studies assessing the BLI technique for IBD dysplasia detection have not been published to date.

Linked-color imaging. LCI was developed in 2014 by Fujifilm (Tokyo, Japan) to further enhance the brightness and image contrast of the BLI system.[29] LCI expands color range by adding red-wavelength information to the green and blue wavelengths for signal processing to produce brighter images than WLE and enhances the contrast for red areas, making the color red more vivid.[26]

There are only case reports on the utility of LCI for the diagnosis of colitis-associated dysplasia published so far.[53] Hisamatsu and colleagues [54] reported cases in which areas initially recognized as indistinct red mucosa under WLI became clearly demarcated as red regions when observed with LCI, leading to a diagnosis of flat-type colitis-associated dysplasia. Kanmura and colleagues also focused on red mucosa with clarified boundaries using LCI, where the addition of indigo carmine spray further emphasized the boundaries of the red mucosa and made the irregularities of lesions clearer. [55]

Texture and color enhancement imaging. Texture and color enhancement imaging (TXI) is a new IEE modality developed by Olympus (Tokyo, Japan) launched in 2020. TXI uses RETINEX theory-based image processing technology to enhance 3 imaging factors in WLE[56]: texture, brightness, and color and facilitates the clear definition of subtle surface irregularities.[44,57] TXI has 2 enhancement modes: TXI mode 1 (texture, brightness, and color enhancement) and TXI mode 2 (texture and brightness enhancement). In TXI mode 1, the color contrast between red and white is greater than that in mode 2, and the mucosa appears more red. TXI mode 2 produces images that are closer to the WLE color tone.

The anticipated utility of TXI based on their features includes (1) improved visibility of superficial digestive tract tumors and (2) enhanced visibility of non-tumorous lesions and biological structures. Promising data have emerged on TXI use for assessment of inflammation in patients with UC; however, only 1 case report has been published for detection of UC-associated neoplasia[58] highlighting the use of TXI Mode 1 in combination with indigo-carmine improved the clarity of lesion boundaries in colitis-associated dysplasia, where CE alone may be insufficient.[53,59] (see **Figs. 1** and **3**).

Ultra-high-definition endoscopy (endomicroscopy and endocytoscopy)

Confocal laser endomicroscopy (CLE) and EC are high-resolution endoscopic imaging techniques that allow a deeper analysis of the intestinal epithelium in real time.[60]

Confocal laser endomicroscopy. CLE is based on tissue illumination with a low-power laser allowing micron-level spatial resolution with $\times$1000 magnification. To obtain images, fluorescence contrast is applied with different agents: fluorescein (10% 5 mL solution, intravenous application), acriflavine hydrochloride, or cresyl violet (topical). Until recently, 2 different CLE systems had been used in clinical endoscopy: a probe-based CLE (pCLE) (Cellvizio, Paris, France), where a probe is delivered in vivo through the endoscope channel, and endoscope-based CLE (eCLE) (Pentax), in which case the probe is fitted at the distal end of a conventional endoscope. The eCLE system is no longer available.

In the lower gastrointestinal (GI) tract, CLE can assist in targeted optical biopsies.[61,62] CLE has been assessed as part of surveillance strategy for IBD-related neoplasia in 2 RCTs, with heterogenous outcomes (**Table 3**). Kiesslich and colleagues, in a study assessing CLE versus conventional WLE for dysplasia detection reported that 4.75-fold more neoplasias were detected in the CLE group (19/23 vs 4/23) and reduced the number of biopsies by 50%. The value of combining CLE with CE was confirmed in subsequent studies.[64–67] In contrast, Freire and colleagues found no improvement

Table 3
Overview of main studies assessing confocal laser endomicroscopy for detection of dysplasia in inflammatory bowel disease

Year, Study	Study Design	Sample Size	Comparators	Se/Sp/Accuracy, %
Kiesslich et al,[61] 2007	RCT	161 UC	eCLE WLE	98.3/94.7/99.2
Hlavati; et al,[62] 2011	Prospective	30 IBD	eCLE DCE	98.4/100 96.8/100
Van der Broek [46] 2011	Prospective	22 UC	pCLE NBI + HD-WLE	65/82/81 100/89/92
Rispo et al,[63] 2012	Prospective	51UC	CLE vs histopathology	100/90/-
Freire et al,[64] 2014	RCT	162 UC	pCLE vs WLE	85.7/97.9/-
Wanders et al,[65] 2016	Prospective cohort	61 CD	eCLE + DCE eCLE	42.9/86.7/92.4 28.6/86.4/80.3
Dlugosz et al,[66] 2016	Prospective	69 PSCIBD	pCLE HD-WLE	89/96/96 68/97/96

Abbreviations: CLE, confocal endomicroscopy; DCE, dye-based chromoendoscopy; eCLE, endoscope-based CLE; HD-WLE, high-definition white-light endoscopy; IBD, inflammatory bowel disease; NBI, narrow-band imaging; RCTs, randomized controlled trials; UC, ulcerative colitis.

in detection rates of dysplasia compared to WLE.[68] CLE was more time-consuming, but reduced the number of biopsies and increased the per-biopsy yield.

In addition, pCLE systems in conjunction with DCE can be used to predict histology of suspected neoplastic lesions with a high diagnostic accuracy as previously reported in a long-term UC cohort by Elhanafi and colleagues. [69] However, at present, CLE cannot be used for surveillance due to availability of newer HD systems, costs, and limited field of view within the colonic mucosa.[21]

Endocytoscopy. EC(Olympus, Tokyo, Japan) is a contact-type optical endoscopy technique that allows real-time histologic assessment of superficial mucosa at ultra-high magnification (× 450–1400). It requires the application of dyes (crystal violet and methylene blue) to assess cellular structures and can discriminate between inflammatory cells.[26]

In the field of IBD, EC was evaluated for histologic disease activity assessment; the use of EC in combination with NBI showed high accuracy in detecting acute inflammation in a UC cohort,[70] as well as a strong correlation with the Geboes score (a system to quantify structural changes and inflammatory activity in colon biopsies) for histologic remission in a different study.[71] Available data are currently limited for IBD surveillance, although this potential role in dysplasia detection has been previously addressed in a case study.[72]

Molecular endoscopy imaging

Molecular imaging is based on the utilization of fluorescent probes with specificity toward defined molecular targets and their visualization by endoscopic devices such as CLE.

Autofluorescence imaging. Autofluorescence imaging (AFI) is an imaging technique that utilizes the properties of a short blue light (400–550 nm) or ultra violet light (<400 nm) to illuminate the mucosa. As a result, biomolecules in tissues ("fluorophores"), consisting mainly of collagen and elastin, emit light of a longer wavelenght

(fluorescent light). The intensity of the fluorescence emission differs between normal and neoplastic tissue.[73] In a head to head comparison of AFI and DCE in a multicenter, non-inferiority RCT (FIND-UC), AFI did not meet predefined performance endpoints compared to DCE for dysplasia detection.[74] This technique is being replaced by fluorescent molecular endoscopy (FME) based on probe-to-binding principle. [75]

Fluorescent molecular endoscopy. This technique allows for applying labeled probes, such as antibodies, against specific target structures in the GI tissue.[16] Major areas of research in IBD currently include detection and characterization of suspected neoplastic lesions and evaluating response to therapies through molecular labeling of drug targets. [76] In a study by Iacucci and colleagues (the Endo-Omics study), successful prediction of treatment response through molecular labeling of drug targets has been achieved; computer-aided pCLE image analysis of crypt and microvascularity architecture and fluorescein leakage can predict response to anti-integrin and anti-TNF treatment in UC and crohn's disease (CD) with 85% and 80% accuracy, respectively.[77] Furthermore, the analysis of mucosal biopsy specimens showed that an increased pre-treatment binding of fluorescent-labeled biologics was associated with a higher likelihood of treatment response in UC.

An animal study on colorectal neoplasm detection in active IBD reports promising data from the fluorescently labeled cathepsin-activated probe 6QC-ICG, which enabled demarcation of premalignant GI lesions in a large animal model. [78] Areas of dysplasia as small as 400 μm were successfully detected 12 to 18 h after an intravenous bolus dose in murine and human-scaled porcine models, and were clearly demarcated within inflamed and ulcerated mucosa. These preclinical results are promising for future clinical FME studies in patients with IBD who suffer from mucosal inflammation and are at high risk of progression to malignant lesions.

ARTIFICIAL INTELLIGENCE IN INFLAMMATORY DISEASE

There are only 2 case reports on detecting IBD-associated dysplasia through an AI system (EndoBRAIN-EYE; Cybernet Systems).[75,79] A pilot study evaluated an AI system for classifying neoplasms occurring in IBD and compared it with the performance of endoscopists.[80] The AI system appeared to perform better than endoscopists, with the diagnostic accuracy of the AI system being 79.0%, compared to 75.8% by non-expert endoscopists and 77.8% by expert endoscopists. Although promising, this is a pilot model and external validation is still required. However, AI holds tremendous potential to address the unmet needs in endoscopic and histologic diagnosis of dysplasia in IBD.[81]

A new deep learning AI model was recently developed for detection and characterization of dysplasia in patients with IBD, with a sensitivity and specificity of 93.5% and 80.6% for lesion detection and 87.5% and 80.6% for lesion characterization, respectively.[82]

SUMMARY

In the last decade, several image-enhancement techniques for GI endoscopy have found their way into clinical practice and have proven to be helpful in several situations. Major updates include the following:

- Although HD-WLE was proven to be superior to SD-WLE, the additional use of CE (dye or virtual) is now recommended as it is supported by exhaustive data.[35]
- Both VCE and DCE are acceptable methods for surveillance colonoscopy in patients with IBD if HD colonoscopy is used; however, it should be performed by

well-trained endoscopists. Additionally, targeted biopsy is sufficient if patients do not present with any high-risk features of CRC development, such as a previous history of neoplasia, tubular colonic morphology, or PSC. This recommendation is also supported by the ESGE guidelines and expert opinion[31]

Significant progress in IEE technology has allowed better detection and management of dysplasia and cancer in IBD. The integration of AI systems is expected to revolutionize the detection and assessment of lesions and improve diagnostic accuracy, potentially also reducing interobserver variability. Additionally, while molecular endoscopy technologies are still in their infancy, they also show promise to enhance our armamentarium for the earlier detection and characterization of concerning pathology.

CLINICS CARE POINTS

- Focus on performing a high-quality colonoscopy. For optimal use of IEE techniques, an excellent field of view should be ensured. Therefore, encourage adequate bowel preparation prior to the procedure.
- Ensure reduction of loops and avoid mucosal trauma as far as possible. To achieve this, consider using a distal attachment; this may help improve lesion detection as well as help with tip stability. This technique may be more effective when combined with the underwater magnification technique.
- Use high-definition endoscopy video equipment
- Any lesion with worrisome features, the borders and the surrounding mucosa should be first assessed in WLE with magnification prior to careful inspection with IEE. High-quality images should be taken for documentation.
- Do not forget to mark the lesion with a sterile carbon particle suspension (tattoo), a single injection 2–3 cm distal (anal side) to the lesion; this will avoid the likelihood of inadvertent spread of the tattoo beneath the lesion and the risk of inducing submucosal fibrosis, which may limit further endoscopic therapy.
- It is of utmost importance that all patients diagnosed with colitis-associated dysplasia be discussed in a multidisciplinary team meeting to achieve consensus on the best management strategy.

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