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Review

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Advanced mucosal imaging in colonoscopy: technical details and clinical applications

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Abstract

Over the past decades, the significant development in endoscopic imaging has revolutionized digestive endoscopy. Real-time optical diagnosis has become possible using different tools and techniques (dye-based and virtual chromoendoscopy) such as narrow band imaging, flexible spectral imaging color enhancement, i-Scan, blue-laser imaging and linked-color imaging. Polyp detection and characterization, and prediction of depth of invasion of colorectal cancers have improved remarkably. Confocal laser endomicroscopy and endocytoscopy have allowed the evaluation of lesions on a cellular level. Not far from the horizon are newer technological innovations such as artificial intelligence and texture and color enhancement imaging that are now being studied for their potential to further improve mucosal visualization, optical diagnosis and virtual histology. This review gives an overview of image-enhanced endoscopy (IEE) and discusses its clinical applications and future directions in the lower gastrointestinal (GI) tract.

Keywords: Image-enhanced endoscopy (IEE), high-definition (HD), white light endoscopy (WLE), narrow-band imaging (NBI), FICE, i-Scan, blue-laser imaging (BLI), linked-color imaging (LCI), confocal laser endomicroscopy, endocytoscopy

INTRODUCTION

Image-enhanced endoscopy (IEE) continues to evolve and has assisted endoscopists in diagnosing

gastrointestinal (GI) diseases. IEE has significantly helped improve the quality of screening colonoscopies, aiding in polyp detection and characterization and predicting the depth of invasion of colorectal cancers. Additionally, it has allowed endoscopists to provide real-time optical diagnosis. Consequently, IEE has reduced unnecessary resections of benign lesions and has played a significant role in deciding whether to perform an endoscopic or surgical resection for the malignant lesions. This review summarizes the different existing IEE techniques and discusses their clinical applications and future directions in the lower GI tract.

GENERAL PRINCIPLES OF IEE

IEE is an endoscopic imaging method used to improve the visualization of mucosal surface patterns and microvasculature features of GI lesions that are even in an early stage[1]. It provides high-contrast endoscopic images of lesions through different dyes and optical and electronic technologies[2]. It has assisted in the endoscopic assessment of neoplastic lesions with greater depth and has enabled subsequent therapeutic decisions to be made with greater precision[3].

IEE can be classified into conventional dye-based chromoendoscopy (CE) and equipment-based methods or virtual CE [Table 1]. In dye-based CE, a dye such as indigo carmine, methylene blue, or crystal violet is applied onto the mucosa as the endoscope is slowly withdrawn while directed to suspicious lesions or the whole colon, such as in surveillance for patients with inflammatory bowel disease (IBD)[6]. The application of dye enhances features of mucosal surface architecture and aids in facilitating the resection of lesions or targeted biopsies of suspicious areas. However, a disadvantage of this technique is that it is often operator-dependent and requires technical expertise in the use of dyes and additional time[7].

Equipment-based methods or virtual CE refers to advanced endoscopic imaging technologies that provide detailed contrast image enhancement of the mucosal epithelium and vasculature through optical filtering of white light or software-driven post-image processing[8]. Narrow Band Imaging (NBI) (Olympus Medical Systems Tokyo, Japan), flexible spectral imaging color enhancement (FICE) (Fujinon, Fujifilm Medical Co, Saitama, Japan), linked color imaging (LCI) (Fujinon, Fujifilm Medical Co, Saitama, Japan), blue light imaging (BLI) (Fujinon, Fujifilm Medical Co, Saitama, Japan), and i-Scan (Pentax Endoscopy, Tokyo, Japan) are examples of this technology. High-definition white light endoscopy (WLE) and magnification endoscopy (ME) also aid in providing high-resolution images and can be considered as part of virtual CE. Compared to using dyes, equipment-based methods have the advantage of ease of use, shorter procedure time, short learning curve, and no need for special assembly or dye[9].

CURRENT RECOMMENDATIONS IN THE USE OF IEE ON COLONOSCOPY

The use of IEE by endoscopists worldwide has rapidly grown, given its numerous advantages over conventional endoscopy. In fact, different societies and groups have advocated its use and its role in assessing GI lesions due to its ability to provide precise visual tissue characterization and accurate prediction of histology. To adapt IEE efficiently in practice, it is suggested that training is necessary to improve performance in the use of the advanced imaging technique[10].

The European Society of Gastrointestinal Endoscopy (ESGE) suggests that advanced endoscopic imaging technologies be used as they can improve mucosal visualization and enhance fine structural and microvascular details[10]. The Asian Novel Bio-Imaging and Intervention Group (ANBI^{2}G), an Asian professional group, also recommends using IEE to enhance the quality of endoscopic diagnosis and improve the detection of early-stage colorectal neoplasia and polyp detection in average-risk patients[1]. Additionally, validated classification systems should be utilized in the advanced endoscopic imaging and optical diagnosis of lesions in the lower GI tract[10].

Table 1. Overview of different IEE techniques and their clinical applicability[3-5]

Technique	Mechanism of IEE	Clinical applications
High-definition white light endoscopy	Signal images with high pixel density (up to millions), allowing visualization of a surface at a 30- to 35-fold magnification	Detection of colorectal neoplasm
Magnifıcation endoscopy	150-fold optical magnification while maintaining image display resolution	Detection or characterization of colorectal neoplasm
Dye-based CE		
- Absorptive dye: crystal violet, methylene blue	Provide sharp detail of cellular surface as the dye is absorbed by specific cells	Characterization and diagnosis of suspicious cancerous lesions
- Contrast dye: indigo carmine	Provide overall detail of the mucosal surface topography when the dye seeps into the crevices and grooves between cells. They do not stain cellular surfaces.	Detection and diagnosis of colorectal neoplasm
Equipment-based CE *Optical digital IEE*		
- Narrow-band imaging (NBI)	Use of two narrow-banded wavelengths of 415 nm (blue light) and 540 nm (green light), which are selectively absorbed by mucosal hemoglobin in the blood to enhance both surface and capillary patterns	Detection, characterization, and diagnosis of colorectal neoplasm
- Flexible spectral imaging color enhancement (FICE)	Computed spectral estimation technology that reconstructs dedicated wavelengths resulting in enhanced visualization of mucosal structures and microvasculature	Detection, characterization, and diagnosis of colorectal neoplasm
- Blue-laser imaging (BLI)	Use of semiconductor laser beams to generate brighter images which enhances the visibility of the superficial mucosal and capillary patterns	Detection, characterization, and diagnosis of colorectal neoplasm
- Linked-color imaging (LCI)	Addition of red-wavelength information in signal processing to produce brighter images comparable to white light imaging	Detection, characterization, and diagnosis of colorectal neoplasm
Equipment-based CE *Digital IEE*		
- I-Scan	Digital post-processing filter technology, which generates high-definition images using three functions: contrast enhancement, surface enhancement, and tone enhancement	Detection, characterization, and diagnosis of colorectal neoplasm
Autofluorescence endoscopy	Highlights endogenous fluorescence generated from tissue by excitation light (370-470 nm) and green light (540-560 nm) radiated sequentially	Detection of colorectal neoplasm
Confocal laser endomicroscopy (CLE)	Image confined to reflected laser light that is refocused via a pinhole	Detection of colorectal neoplasm in IBD
Endocytoscopy	Ultra-high magnified white light images (520×) through a high-power fixed-focus objective lens	Detection and characterization of colorectal neoplasm

In patients with IBD, IEE is recommended as it improves the detection of dysplasia[1]. To characterize colorectal lesions in this subset of patients, ANBI^{2}G recommends macroscopic classification using indigo carmine spray. The application of dye unmasks flat lesions and the borders and surface contours become better visible[11]. The ESGE and the British Society of Gastroenterology (BSG) recommend CE with targeted biopsies as the surveillance method in patients with IBD[12]. On the other hand, the American Gastroenterological Association (AGA) and the American Society for Gastrointestinal Endoscopy (ASGE) endorse the use of IEE with HD colonoscopy as surveillance for persons with long-term colonic IBD[13,14]. This was part of the SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations) international consensus statements published in 2015[15].

IMAGE-ENHANCED ENDOSCOPY TECHNIQUES IN THE LOWER GI TRACT

Dye-based chromoendoscopy

Dye-based CE aids the endoscopist in the detection and characterization of lesions in the GI tract with the application of dyes or stains. It can enhance lesion discrimination by highlighting the mucosal surface and light-absorptive patterns[16]. The topical staining agents used are considered generally safe except for those with known prior allergic reactions[17]. It is often applied with spraying catheters producing a fine mist onto the GI tract surface. While the endoscope is slowly withdrawn, dye is sprayed through the endoscope tip as the scope is directed onto the mucosa in a spiral motion[6]. As the effect of dye is only transient, short

segments of approximately 20 cm should be stained each time, followed by a careful inspection. The staining solution can be applied through nontargeted pancolonic CE or targeted CE directed toward suspicious visible abnormalities[17]. It is important to note that good bowel preparation is critical when using dye-based CE in the lower GI tract. Anti-spasmodic agents can also be used to minimize bowel peristalsis that could lead to uneven dye distribution.

Dyes used in the evaluation of colonic lesions can be classified into two major categories: absorptive dyes and contrast dyes. Absorptive dyes allow sharp detail of cellular surface as it is absorbed by specific cells[6]. An example is crystal violet which stains epithelial cells in the colonic mucosal glands, making the pit look white after dyeing. Staining usually takes 2 to 3 minutes after the dye is sprayed onto the colonic mucosa. Methylene blue is another example of an absorptive dye. It stains the epithelial cells of the small or large intestine blue, as opposed to dysplastic lesions, which remain unstained[17]. A more practical and less time-consuming approach has been studied using Methylene blue in tablet form. If given orally (MB-MMX 200 mg) with bowel preparation agents, it has shown the potential to increase the adenoma detection rate[18].

Contrast or non-absorptive dyes provide detail of the mucosal surface contour when the dye seeps into the crevices and grooves between cells. Contrast dyes do not stain cellular surfaces. An example of this is indigo carmine, a dark blue stain, which can enhance the contrast of raised and deepened areas and highlight the topography of the mucosal surface, leading to improved detection of neoplastic lesions. It is useful to differentiate between benign and malignant lesions, delineate borders of early-stage neoplastic lesions, and estimate the depth of invasion of cancers[2]. It is generally used at a concentration of 0.1%-0.5%[5].

When applying dyes, staining pit patterns can be categorized according to different classification systems, such as the Kudo pit pattern classification. Endoscopic polyp appearance can be characterized by the colonic mucosal pit pattern following the application of a dye[19]. Neoplastic tissue demonstrates irregular, tubular, or villous pits, whereas non-neoplastic tissue with rounded or stellar pits.

Equipment-based chromoendoscopy

High-definition white light endoscopy and magnification endoscopy

High-definition white light endoscopy (HD WLE) and magnification endoscopy (ME) are categorized as IEE as they can produce high-resolution images that aid in the evaluation of the mucosal surfaces and subtle changes in lesions. In HD WLE, the endoscope produces signal images with higher pixel densities up to millions, allowing visualization of a surface at a 30- to 35-fold magnification[3]. It also has faster line scanning on the monitor, resulting in sharper images with fewer artifacts. In HD WLE, optical zooming can be done by positioning the optical lens at the tip of the endoscope very close to the mucosal surface to control focal distance. With a closer distance, subtle changes in lesions can be examined.

In contrast to HD WLE, ME can examine changes in the mucosal microstructure and microvasculature by providing 150-fold magnification while maintaining image display resolution. As a result, more surface details, including pit patterns and vascular details, can be assessed. At times, ME also allows histological diagnosis of a lesion by endoscopic visualization. The use of a distal transparent cap attachment can facilitate magnification as it helps control and stabilize the short distance from the optical lens to the mucosa[20].

Narrow band imaging

Narrow band imaging (NBI) is an endoscopic optical image enhancement technology developed by Olympus Medical Systems, which works through optical filters and the principle of light penetration. With a

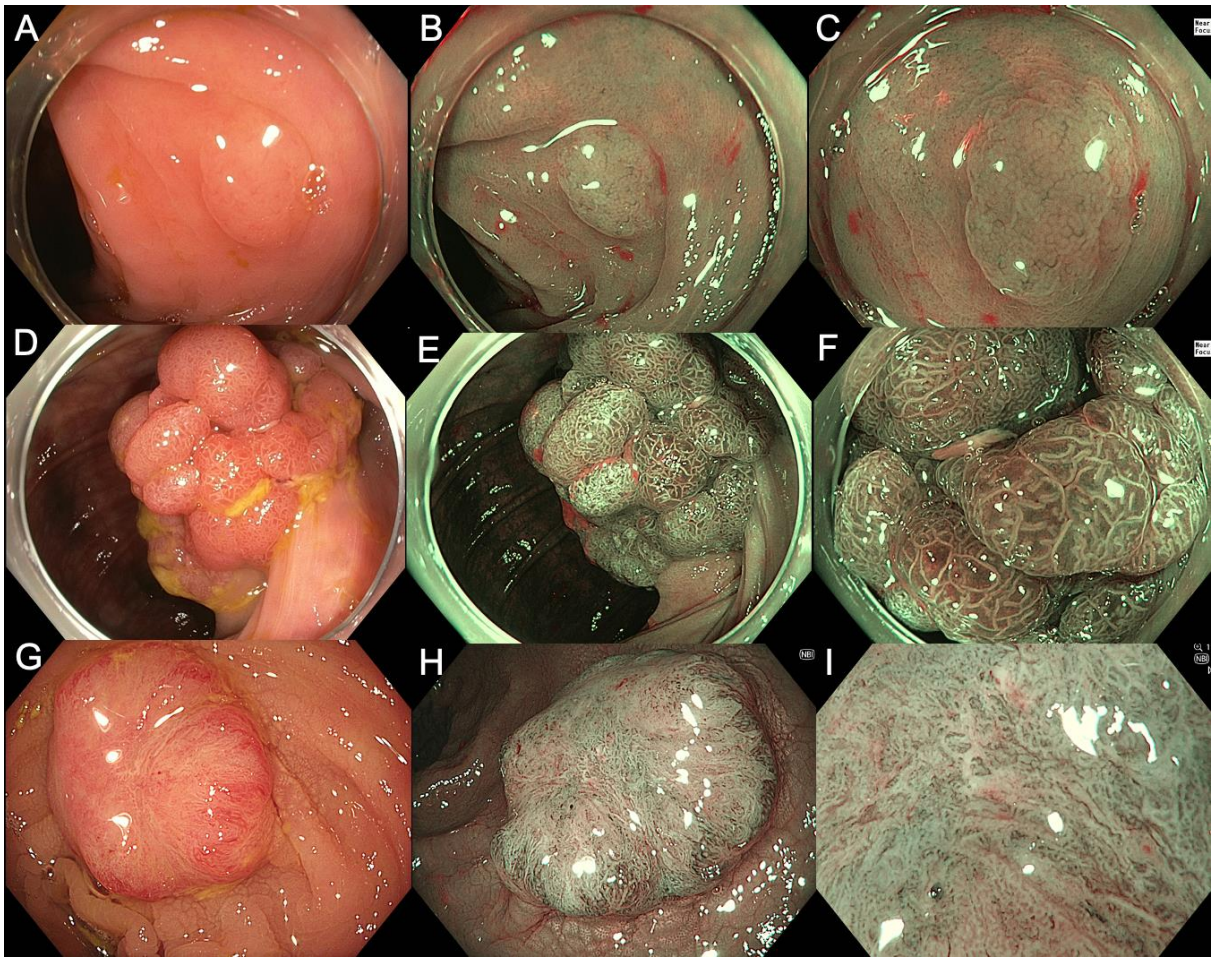

Figure 1. White light, narrow band imaging, and magnification endoscopy of colorectal polyps. Hyperplastic polyp NICE 1, JNET Type 1, MS I on (A) WLE, (B) NBI, and (C) Magnification NBI. Adenomatous polyp NICE 2, JNET Type 2A, MS II on (D) WLE, (E) NBI, and (F) Magnification NBI. Malignant polyp (invasive adenocarcinoma) NICE 3, JNET Type 3, MS IIIb on (G) WLE, (H) NBI, and (I) Magnification NBI. NICE: Narrow-band imaging international colorectal endoscopic classification; JNET: Japan NBI expert team; MS: modified Sano; WLE: white light endoscopy; NBI: narrow-band imaging.

special optical filter, it uses two narrow-banded wavelengths of 415 ± 15 nm (blue light) and 540 ± 15 nm (green light), which are selectively absorbed by mucosal hemoglobin in the blood[21]. This results in the marked enhancement of capillaries and micropatterns in the mucosal surface layer[22]. Capillaries in the superficial mucosa appear brown when highlighted by the 415 nm wavelength, while deeper veins appear blue-green (cyan) when the 540 nm wavelength penetrates. This contrasts with the nonvascular structures in the mucosa[10].

NBI markedly improves the visualization of cancerous tissues characterized by abnormal surface and vascular patterns [Figure 1]. This is important in GI screening for early colorectal cancers[23]. If combined with ME, visualization of lesions is further improved, making the assessment of mucosal microstructure and microvasculature clearer and more accurate[2].

Several magnifying NBI observation classification systems for colorectal tumors have been developed. These classification systems aid lesion characterization and therapeutic decision-making if endoscopic resection is possible. The most used ones are the NBI International Colorectal Endoscopic (NICE) classification

proposed in 2009 [Table 2] and the Japan NBI Expert Team (JNET) classification developed in 2014 [Table 3]. The NICE classification is based on the visualized color, vessels, and surface pattern of the colorectal tumor. Given these characteristics, the lesion is classified into three types, which also predict the most likely histology of the lesion - hyperplastic, adenoma, or deep submucosal invasive cancer. Different international studies have validated its usefulness in diagnosing colorectal polyp histology and predicting the depth of carcinoma invasion[24-26].

The JNET classification is based on the visualized vessel and surface pattern of colorectal lesions on NBI. It was proposed based on the consensus of selected NBI specialists, establishing a universal NBI magnifying endoscopic classification[25]. Like NICE, it is also predictive of the most likely histology of the lesion; however, it has further classified adenomatous lesions as possible low-grade intramucosal neoplasia (Type 2A) and lesions that may be of high grade or with shallow submucosal invasive cancer (Type 2B).

Another NBI-based classification system is the modified Sano's (MS) classification [Table 4], which defines colorectal tumors in accordance with the color, capillary network surrounding the pit pattern and surface pattern evaluated under magnification. In the MS classification, a separate sub-classification for sessile serrated adenoma/polyp (SSA/P) is included[27-29].

i-Scan

i-Scan is a software-based digital post-processing filter technology developed by Pentax Endoscopy (Tokyo, Japan). It produces high-definition images using image enhancement functions, namely contrast enhancement (C/E), surface enhancement (S/E), and tone enhancement (T/E)[30]. The C/E mode sharpens the views of surface vessels and increases the visibility of depressed lesions with the enhancement of blue light and suppression of the red and green light components. The S/E mode increases the light and dark color contrast, enhancing the visualization of mucosal surface texture and inspection of subtle mucosal changes. The T/E mode increases the contrast between the mucosa and blood vessels by dividing images obtained using normal white light into red, green and blue (RGB) components. This is then converted and resynthesized into a new image in which vascular patterns or subtle mucosal irregularities are highlighted, thereby improving visibility[2,30].

Flexible spectral imaging color enhancement

Flexible spectral imaging color enhancement (FICE), also known as Fujinon intelligent chromoendoscopy, is a computed spectral estimation technology developed by Fujifilm (Tokyo, Japan). It is a software-driven digital imaging post-processing system that reconstructs dedicated wavelengths resulting in enhanced visualization of mucosal structures and microvasculature[31]. Using an image processing algorithm, it can produce a composite computerized virtual chromoendoscopy enhanced color image using 60 types of spectral images between 400 and 695 nm wavelengths at 5 nm intervals[32].

Blue laser/light imaging

Blue laser imaging (BLI) system is an endoscopy system developed by Fujifilm (Kanagawa, Japan) to address FICE's limitation in producing bright and high-contrast images[9]. BLI is made of the LASEREO endoscope system, which utilizes semiconductor laser beams (4-light-emitting diode multi-light system) as the light source compared to the conventional xenon light. This technology produces brighter images, improving the visibility of both the superficial mucosal and microvascular patterns. The 410 nm narrow-band laser light source (410 ± 10 nm) produces a narrow spectrum that enhances the microvasculature to visualize subtle changes in the mucosal surface, whereas the 450 nm laser light source provides white light illumination[2,8]. In 2016, Fujifilm released blue light imaging (also called BLI) to cater to some areas where LASER

Table 2. Narrow-band imaging international colorectal endoscopic classification (NICE)[24]

Characteristic	NICE 1	NICE 2	NICE 3
Color	Same or lighter than background	Brown relative to background	Brown to dark brown relative to background; occasional white patches
Vessels	None or lacy vessels along surface	Thick brown vessels surrounding white structures or dots	Areas of markedly distorted vessels (varying thickness and irregular pattern) or absence of vessel pattern
Surface pattern	Dark spots surrounded by white	Oval, tubular, or branched white structures bordered by brown vessels	Distortion or absence of pattern
Most likely pathology	Hyperplastic or sessile serrated lesion	Adenoma	Submucosal invasive cancer

From Hayashi *et al.*[24] (Permission for publication obtained).

Table 3. Japan NBI expert team (JNET) classification[25]

	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	Invisible[*1]	Regular caliber Regular distribution (meshed/spiral pattern)[*2]	Variable caliber Irregular distribution	Loose vessel areas Interruption of thick vessels
Surface pattern	Regular dark or white spots Similar to surrounding normal mucosa	Regular (tubular/branched/papillary)	Irregular or obscure	Amorphous areas
Most likely histology	Hyperplastic polyp/Sessile serrated polyp	Low grade intramucosal neoplasia	High grade intramucosal neoplasia/Shallow submucosal invasive cancer[*3]	Deep submucosal invasive cancer

From Sano *et al.*[25] (Permission for publication obtained). [*1]If visible, the caliber in the lesion is similar to the surrounding normal mucosa; [*2]micro-vessels are often distributed in a punctate pattern and well-ordered reticular or spiral vessels may not be observed in depressed lesions; [*3]deep submucosal invasive cancer may be included

Table 4. Modified Sano's classification[27]

MS classification	Predicted histology	Description
Category I	Hyperplastic (HP)	Pale color ± round pits with central brown star-like dots or bland appearance ± minute capillaries that may meander across polyp
Category IIo	Sessile serrated adenoma/polyp (SSA/P)	Pale or light dark color ± open pits ± 3 out of 5: cloud-like surface, inconspicuous margins, mucous cap, irregular shape and varicose microvascular vessels[1]
Category II	Tubular adenoma with low-grade dysplasia	Light dark or dark color ± white linear or oval pits ± linear or oval regular capillary network surrounding pits
Category IIIa	High-grade dysplasia[2]/villous or tubulovillous adenoma/superficial cancer	Light dark or dark color ± white villous/cerebriform pits ± tortuous/branched mildly regular capillary network surrounding pits[3]
Category IIIb	Invasive cancer	Dark surroundings with pale central area ± loss of pits and vascular pattern

From Zorron Cheng Tao Pu *et al.*[27](Permission for publication obtained). [1]If no open pits and two serrated features = classified as low confidence for SSA/P; if one serrated feature = low confidence for HP; if no features = high confidence for HP; [2]high-grade dysplastic SSA/Ps are included in this category; [3]can have a slight loss of pit pattern and vascularity when leaning towards superficial cancer.

endoscopes have not been approved for use. This variation uses a four-light emitting diode (LED) as a light source instead of LASER[33].

BLI provides high-contrast images using three modes: (I) BLI mode for detailed magnified observation; (II) BLI bright mode to visualize both surface and vascular patterns even from a distant view; and (III) white light mode which uses a 450-nm laser to better enhance the microvasculature[8]. The Hiroshima classification system to delineate lesions was developed using BLI [Table 5]. It characterizes colorectal

Table 5. Hiroshima classification of colorectal polyps[25]

Type		Description
A		Microvessel intensity is vague or invisible None or isolated lacy vessels may be present coursing across the lesion. Brown or black dots, start or round shaped surrounded by white
B		Regular surface pattern is observed by the increased microvessel intensity around the pits and enhanced image. Or regular meshed microvessel network pattern is observed
C	1	Irregular surface pattern is observed by the increased microvessel intensity around the pits and enhanced image. Thickness and distribution of vessels are homogeneous
	2	A more irregular surface pattern is observed by the increased microvessel intensity around the pits and enhanced image Thickness and distribution of vessels are heterogeneous
	3	Surface pattern is completely unclear Thickness and distribution of vessels are heterogeneous Avascular areas (AVA) and scattered microvascular fragments are observed

From Sano *et al.* [25] (Permission for publication obtained).

polyps using both surface and vascular patterns. In this classification, type A describes non-adenomatous polyps, type B describes adenomatous polyps, type C1 describes intramucosal carcinoma, and type C3 describes deep submucosal invasion[8,25].

Linked color imaging

In 2014, Fujifilm developed linked color imaging (LCI) to further enhance the brightness and image contrast of the BLI system. In LCI, red-wavelength information was added to the green and blue wavelengths for signal processing to produce brighter images comparable to white light imaging[34]. In addition, LCI differentiates the red color spectrum by a unique image processing to produce increased color contrast making red regions more vivid[8]. This results in increased detection and accurate delineation of colorectal lesions.

Autofluorescence imaging

Autofluorescence imaging (AFI) is an endoscopic system developed by Olympus that highlights endogenous fluorescence generated from tissues by excitation light[35,36]. In AFI, excitation light (370-470 nm) and green light (540-560 nm) are radiated sequentially in autofluorescence mode[3]. This wide-field red-flag technology can potentially aid in the detection of dysplasia or early cancer displayed on the pseudo-color image as magenta. Nevertheless, due to inconsistent efficacy results in several studies, the overall benefit of AFI currently appears limited to the research setting[31].

Confocal laser endomicroscopy and endocytoscopy

Confocal laser endomicroscopy (CLE) and endocytoscopy are advanced endoscopic imaging technologies that provide higher-resolution, cellular-level views of gastrointestinal epithelia in real-time[3]. Using these technologies, the histological structure of the colonic epithelium can be recognized and evaluated.

In CLE, an image resolution is markedly increased through the confinement of an image to reflected laser light that is refocused using a source pinhole[37]. To allow tissue excitation and further achieve a higher resolution, topical or intravenous fluorescence dyes can be used to enhance the cellular, subcellular and vessel architecture. There are two different CLE systems in clinical endoscopy, namely probe-based CLE (pCLE) and endoscope-based CLE (eCLE). In pCLE, a probe is delivered in vivo through the endoscope channel, whereas in eCLE, the probe is fitted at the distal end of a conventional endoscope. In the lower GI tract, CLE can assist in targeted optical biopsies[38]. Several studies have shown that it has moderate to high diagnostic accuracy in the evaluation of colonic polyps and the characterization of colorectal lesions in IBD[39,40].

Endocytoscopy generates ultra-high magnified white light images (520x) through a high-power fixed-focus objective lens in real-time[41]. In this technique, cellular structures are visualized in vivo with the application of crystal violet and methylene blue, which stains the cell stroma and nucleus[42,43]. As endocytoscopy can provide real-time cellular imaging, its utility includes the characterization and depth assessment of dysplastic or early cancerous lesions of the GI tract and their histological differentiation.

CLINICAL APPLICATIONS

Adenoma detection rate and polyp detection

High-definition imaging has resulted in an overall improvement in adenoma detection[16]. Studies have shown that newer IEE technology can potentially better enhance polyp detection by highlighting lesion characteristics. This is particularly significant as early detection can effectively avert colorectal cancer (CRC) and its related mortality. However, to date, different IEE techniques have heterogeneous evidence for adenoma detection.

Since the development of the first-generation NBI in 2005, consistent results have shown that the overall adenoma detection rate (ADR) was just the same when comparing first-generation NBI and WLE[44,45]. However, with the second-generation NBI introduced in 2012, where brighter images can be achieved, its benefits for adenoma detection were noted to be more evident. A recent meta-analysis of 4,491 individual patients in 11 randomized controlled trials (RCT) showed that second-generation NBI has a better ADR than WLE (OR: 1.28; 95%CI: 1.05-1.56; $P = 0.02$)[46]. Overall, including the trials using the first-generation NBI, the ADR was 45.2% for NBI *vs.* 42.3% for HD-WLE (OR for adenoma detection of 1.14 NBI *vs.* HD-WLE; 95%CI: 1.01-1.29; $P = 0.02$).

The utility of i-Scan in improving ADR had contradictory results. A meta-analysis of five RCTs showed no significant difference in the ADR of i-Scan T/E mode and WLE (RR: 1.09; 95%CI: 0.97-1.23)[47]. In contrast, an RCT comparing the ADR between HD i-Scan S/E mode and SD-WLE revealed that the use of i-Scan had a significantly higher ADR (38% *vs.* 13%; $P < 0.0001$)[48]. A more recent RCT by Kidambi *et al.* has also shown that i-Scan (S/E + C/E mode) has a higher ADR compared to HD-WLE (47.6% *vs.* 37.2%; $P = 0.005$)[49].

Given its dark image, Fujifilm's FICE has shown no benefit in the improvement of overall ADR[50,51]. However, with the development of the newer IEE mode BLI that produces a brighter image, its benefit in enhancing polyp detection was more definite, although the study results had been inconsistent. A small RCT in Singapore has shown that BLI-bright could enhance ADR compared to HD-WLE (46.2% *vs.* 27.8%; $P = 0.010$)[52]. In addition, a tandem endoscopy study by Shimoda *et al.* has shown that BLI had a lower colon adenoma miss rate compared to HD-WLE (1.6% *vs.* 10%; $P = 0.001$)[53]. In contrast, an earlier study showed that BLI-bright mode could make polyps more visible but with no improvement in ADR compared to WLE (54.8% *vs.* 52.7%; $P = 0.52$)[54].

With the enhanced brightness and image contrast, Fujifilm's LCI has shown more favorable evidence for the improvement of ADR. Study results were more consistent when comparing the ADR of LCI over HD-WLE. A multicenter, randomized, crossover trial has shown that LCI was associated with higher ADR compared to HD-WLE (37% *vs.* 29%; $P = 0.001$)[55]. Another study by Paggi *et al.* demonstrated that LCI improves the ADR and decreases the polyp miss rate in the right colon (OR: 0.25; 95%CI: 0.11-0.56)[56]. Their group also published an RCT in which LCI is associated with a higher ADR compared to HD-WLE amongst the FIT-positive population in a CRC-screening program[57]. Finally, a recently published meta-analysis of seven RCTs has concluded that LCI could significantly improve ADR compared to WLE (RR: 1.26;

95%CI: 1.14-1.39; $P < 0.001$)[58].

Polyp characterization and histology prediction

Both dye-based and equipment-based IEE have been shown to be promising tools for the characterization of colorectal polyps and real-time prediction of their histology[16]. Dye-based CE can highlight the surface pattern of polyps, and its histology can be reliably predicted using the Kudo pit pattern classification for colonic lesions[19,59]. Non-neoplastic lesions can be classified as Type 1 (round pits) and Type II (stellate pits), whereas neoplastic lesions can be classified as Type III (tubular pits), Type IV (gyros-like pits), and Type V (irregular pits). A meta-analysis has shown that the Kudo pit pattern classification can predict neoplastic *vs.* non-neoplastic lesions with a sensitivity of 92% and specificity of 94%[60].

The use of equipment-based IEE has also been shown to aid in the characterization of polyps and the prediction of histology of benign and neoplastic lesions. In a meta-analysis of 28 studies, NBI has been shown to accurately differentiate neoplastic from non-neoplastic lesions with a high sensitivity and negative predictive value (NPV) greater than 90%[61]. I-Scan can also predict histology with a sensitivity of 98% and specificity of 93%[48]. Similarly, FICE was shown to have a high sensitivity of 93% and NPV of 85% in distinguishing neoplastic from non-neoplastic colorectal lesions[62].

The utility of equipment-based IEE may permit a predict-resect-and-discard approach[63]. However, this strategy has several drawbacks. For instance, this approach may not be appropriate for larger polyps as evidence only recommends its use for diminutive polyps where the risk of advanced neoplasia is very low[64,65]. Likewise, identification of serrated lesions despite being classified as JNET type 1 or NICE type 1 on IEE should not preclude the use of a resect-and-discard strategy as these lesions are associated with a higher risk of advanced neoplasia. Given these criticisms, while IEE can aid in the prediction of underlying histology, it is important to consider other polyp factors such as size, site, and morphology before considering a resect-and-discard approach.

Endocytoscopy is another modality with the potential to predict polyp histology. According to an RCT by Mori *et al.*, endocytoscopy is noninferior to standard biopsy for the discrimination of neoplastic lesions, which supports using endocytoscopy as a novel alternative to standard biopsy in routine colonoscopy[66]. However, the technology is not widely available and has struggled to make inroads in routine clinical practice.

Prediction of the depth of invasion

The depth of invasion of a colorectal neoplasm can be predicted by endoscopic visualization of the lesion through WLE. In Japan's national colorectal cancer screening program, submucosal invasion is significantly higher for non-polypoid lesions compared to polypoid types (42.4% *vs.* 21.0%)[67]. However, given the nature of these non-polypoid lesions, which are often subtle and flat, their detection remains a challenge.

Few studies have shown the potential of IEE in predicting the depth of invasion of a colorectal neoplasm. Dye-based CE with magnification can identify neoplastic invasive patterns and can aid in differentiating superficial or intramucosal submucosal cancers from deep submucosal cancers[68,69]. Virtual CE can also predict the risk of invasive cancer in suspected lesions[70]. The utility of NBI in predicting the depth of invasion was first described by Hirata *et al.*, who noted that vessel thickness and microvascular density (meshed capillary vessels, vascular pattern intensity, or brown hue) are predictive of tumor invasion[71]. This knowledge has led to the development of the NICE classification system, which is based on visualized vessels, color, and surface patterns of colonic polyps [Table 2][24]. It had a high accuracy of 89%, sensitivity of

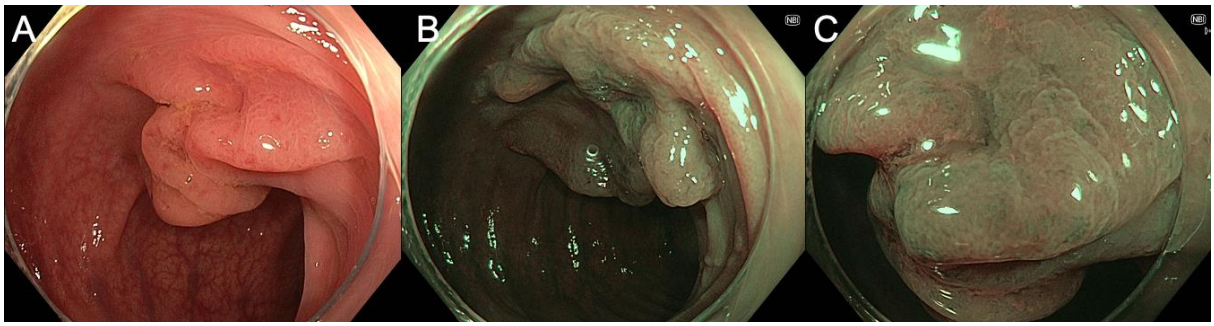

Figure 2. Sessile serrated lesion in the descending colon, NICE 1, JNET Type 1, MS IIo, on (A) WLE, (B) NBI, and (C) Magnification NBI. NICE: Narrow-band imaging international colorectal endoscopic classification; JNET: Japan NBI expert team; MS: modified Sano; WLE: white light endoscopy; NBI: narrow-band imaging.

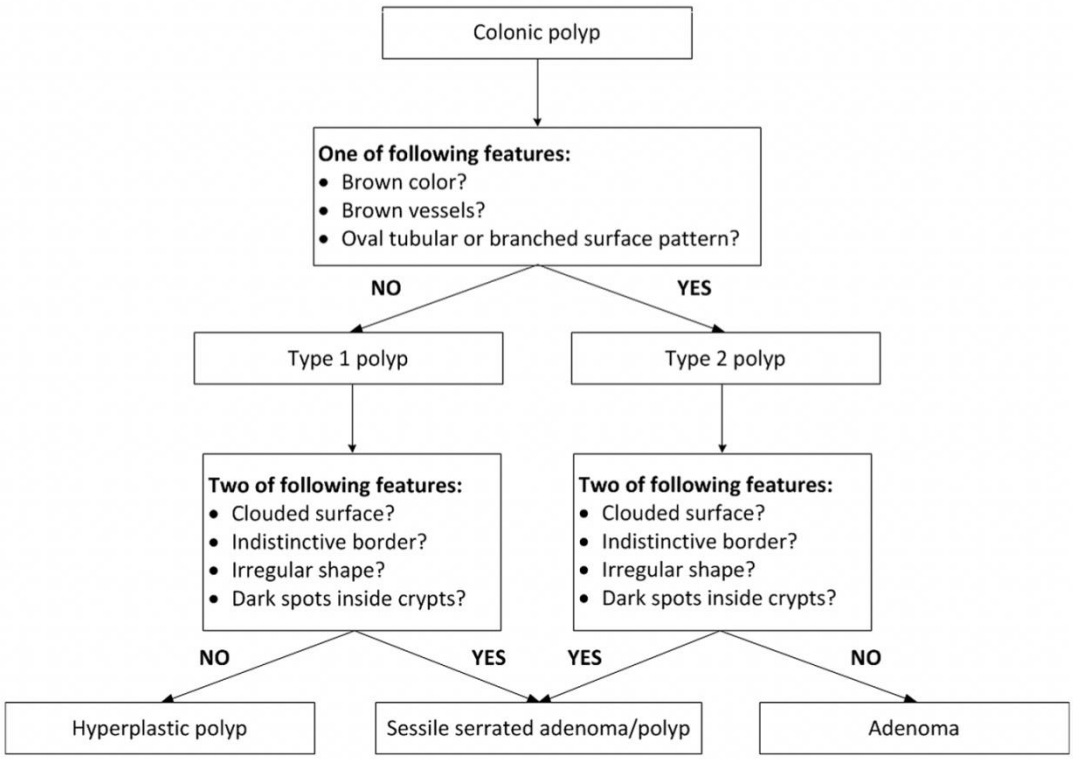

Figure 3. WASP criteria: features of sessile serrated lesions (SSL), hyperplastic polyps, and adenomatous polyps. NICE: NBI international colorectal endoscopic classification; NBI: narrow band imaging. From IJspeert JE *et al.*[74] (Permission for publication obtained).

98%, and NPV of 95% in diagnosing small colorectal polyps[26]. A more recent classification system developed by Japanese endoscopists is the JNET classification[25]. This subdivides NICE type 2 (adenomatous lesions) into JNET type 2A (low-grade adenomas) and JNET type 2B (high-grade adenomas and shallow submucosally invasive cancer). However, its performance is limited in the differentiation of superficial and invasive cancer types (e.g., JNET type 2B and 3).

Endocytoscopy also proves to have a high diagnostic accuracy in predicting deep submucosal invasion compared to pit pattern diagnosis (OR: 1.31; 95%CI: 1.00-1.71; I2 = 0%; P = 0.05) based on a meta-analysis[72]. However, selection bias could be possible because the four studies included in the analysis were all retrospective.

Evaluating sessile serrated lesions

Sessile serrated lesions (SSL) are recognized as antecedent lesions of colorectal cancer [Figure 2][73]. With the aid of IEE, four SSL-like features can be described, namely, clouded surface, indistinctive border, irregular shape, and dark spots inside the crypts. These constitute the 'Workgroup serrated polypS and Polyposis' (WASP) classification, in which the presence of at least two features is considered sufficient to diagnose an SSL [Figure 3]. This classification system was validated with a high pooled accuracy of 84% and a pooled NPV of 91% for diminutive neoplastic lesions[74].

Utility in inflammatory bowel disease

Dysplastic lesions in IBD can be difficult to detect because they often have subtle and flat characteristics[75]. As these lesions could be precursors to colorectal cancer, it is important to identify them on screening or surveillance colonoscopies, especially for high-risk patients with long-term IBD. To increase the yield of colorectal dysplasia detection, there are pieces of evidence supporting the use of dye-based pancolonic CE with targeted biopsy *vs.* standard definition WLE with random biopsies[16,76,77]. A study by Kiesslich *et al.* showed that pancolonic CE results in a significant 3.2-fold increase in dysplasia detection[40]. CE is now the recommended standard of care in international guidelines[15,78,79].

Equipment-based CE techniques have been shown to have evolving benefits in IBD. Compared to NBI, there was initially an insignificant trend in favor of dye-based CE for dysplasia detection in patients with long-standing IBD[80]. However, a large randomized prospective study by Bisschops *et al.* showed that CE and NBI do not differ significantly in the detection of colitis-associated neoplasia[81]. Given the easier technique, NBI may possibly replace dye-based CE in these settings. The newer IEE technologies, such as i-Scan, FICE, and BLI, have no available data in the context of colitis surveillance[1].

PRACTICAL RECOMMENDATIONS FOR CLINICAL APPLICATION

For optimal utilization of IEE, an excellent field of view should be ensured. The entire colonic mucosa should be well visualized with no residual staining, stool fragments, liquid, gas bubbles or blood. Washing the field until clear may take more time than performing the advanced mucosal imaging technique itself. Hence, adequate bowel preparation should be advised prior to the colonoscopy. Simethicone may be flushed on areas with gas bubbles to lower their surface tension. Loop formation during scope insertion or any mucosal trauma should be avoided as far as possible. The use of a transparent cap during colonoscopy has been shown to improve polyp detection rates and might also contribute to colonoscope tip stability and may also help when combined with the underwater magnification technique[82].

Based on the current level of evidence and the applicability of the different IEE technologies, we suggest that the entire colonic lesion and the surrounding mucosa should be initially inspected with WLE, followed by careful inspection with IEE. Optical magnification is easy and only takes a short time when assessing colonic lesions. Any areas within the lesion that appears to harbor worrisome features (e.g., depression, suspected pit, or vascularity distortion) should be further inspected with magnification. High-quality images should be taken for documentation. Moreover, assessment of the margins of the lesion is paramount, especially in sessile serrated lesions where the inconspicuous margins might be assessed more clearly with IEE. IEE with magnification should also be performed before and after polyp resection to delineate lesion borders and to

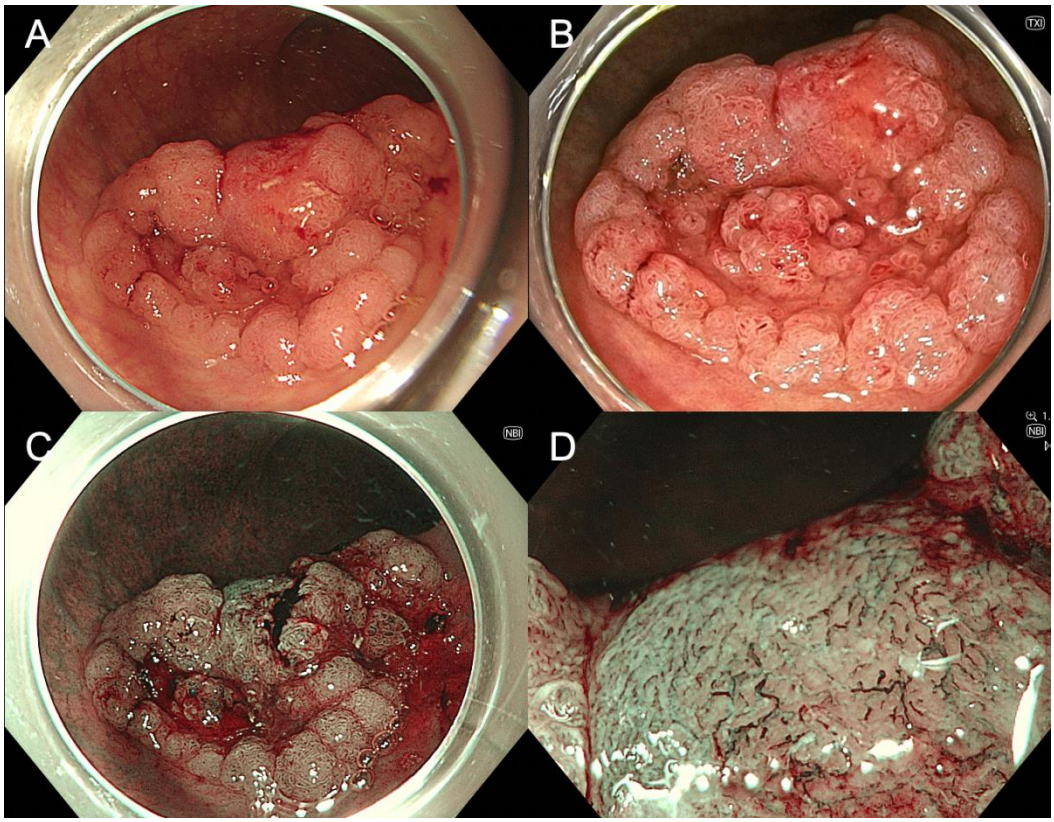

Figure 4. Rectal polyp measuring 3.5 cm, Paris IIa + 1s, NICE 3, JNET Type 2B, MS IIIa, on (A) WLE, (B) TXI, (C) NBI, and (D) Magnification NBI.

ensure complete resection. As for surveillance of patients with IBD, WLE could be used during the progression of the scope to the cecum and IEE during scope withdrawal.

Given the relative availability of the different advanced technologies, it is recommended that endoscopists should make every effort to improve their performances whenever possible. The ESGE has suggested that training on advanced endoscopic imaging be a prerequisite for its use in clinical practice for improved performance[10].

NEWER DIRECTIONS AND ADVANCEMENTS

Optivista is a new IEE mode introduced by Pentax in 2016. It is based on the use of a mechanical optical filter that generates bandwidth-limiting light to improve mucosal surface and vascular characterization of colorectal polyps[5]. A recent study demonstrated that Optivista has a similar ADR with the older Pentax IEE technology i-Scan (39.4% *vs.* 38.3%, $P = 0.82$)[83]. Other data including a direct comparison to WLE remains lacking.

In 2020, Olympus introduced Texture and Color Enhancement Imaging (TXI). In TXI, three image factors in WLE, namely texture, brightness, and color, are enhanced to clearly define subtle tissue differences [Figure 4][84]. The images obtained under normal white light are divided into a texture image and a base image. These two images are then recombined to enhance the structure, color tone, and brightness of the mucosal surface[5]. A recent study of 27 patients in Japan showed that TXI provided higher visibility than WLE for colorectal polyps, including SSLs[85]. Another study of 22 Japanese patients with 68 lesions also

showed TXI enables improved visualization of colorectal lesions than WLE and NBI (TXI mode1 80.5, TXI mode2 75.6, WLE 70.0, NBI 69.0)[86]. Several studies are currently in progress to determine TXI's efficacy in improving detection rates in colonoscopy.

Red dichromatic imaging (RDI) is a new IEE technology developed by Olympus, which can enhance the visibility of deep blood vessels using green (540 nm), amber (600 nm), and red (630 nm) wavelengths[87]. Hemoglobin can absorb different wavelengths, leading to the identification of possible bleeding points. RDI has three modes, with mode 1 helpful in visualizing bleeding points, whereas modes 2 and 3 in visualizing deep and superficial vessels. To date, limited published data on RDI exists. A study by Hirai *et al.* has shown that RDI improves the detection of bleeding points in acute GI bleeding compared to WLE (3.12 ± 0.51 *vs.* 2.72 ± 0.50; $P < 0.001$)[88]. Recent case reports have also shown its efficacy in reducing the risk of bleeding in endoscopic submucosal dissection (ESD) and per-oral endoscopic myotomy (POEM)[89,90].

Computer-aided detection (CADe) using artificial intelligence (AI) for colonoscopy is a newer technology being developed and studied to improve ADR and allow pathological prediction of detected colorectal lesions[91]. A prospective, RCT by Repici *et al.* has shown that computer-aided detection (CADe) (GI Genius, Medtronic) during colonoscopy increases ADR when compared with the control group (53.3% *vs.* 44.5%; RR: 1.22, 95%CI: 1.04-1.40; $P < 0.01$ for non-inferiority and $P = 0.02$ for superiority)[92]. A recent network meta-analysis of 50 RCTs, comprising 34,445 participants, has also shown that ADR was higher with CADe by 7.4% (OR: 1.78; 95%CI: 1.44-2.18) and higher with chromoendoscopy by 4.4% (OR: 1.22; 95%CI: 1.08-1.39) compared with WLE[93].

Aside from polyp identification, AI has also been studied to provide real-time in vivo computer-aided diagnoses (CADx) of neoplastic *vs.* non-neoplastic lesions[94]. In a recent study of 60 colorectal polyps assessed with CADx *vs.* intuitive optical diagnosis, CADx had a diagnostic accuracy of 88.3% using high-definition WL images and 86.7% using BLI images[95]. In a multicenter library of > 200,000 images from 1572 polyps, CADx had a sensitivity, specificity, and accuracy of 85%, 79%, and 84%, respectively[96].

CONCLUSION

The advancements in IEE technology have allowed better detection and management of colorectal cancers and other pre-malignant conditions. It has played distinctive roles in polyp and histologic characterization and prediction of depth of invasion of colorectal cancers, thereby improving clinical outcomes. With the advent of tools such as AI and newer IEE modes, detection rates can potentially be further improved and promising future directions such as the resect-and-discard strategy of diminutive polyps, prediction of histology of difficult polyps such as sessile serrated lesions, and AI-driven prediction of depth of invasion of colorectal cancers can come to fruition. Growing research in this area could significantly impact the diagnostic and therapeutic process in GI endoscopy.

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Author's contributions

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