The Role of Chromoendoscopy in Evaluating Colorectal Dysplasia

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Abstract: Chromoendoscopy pertains to image-enhanced endoscopic techniques such as dye-based chromoendoscopy and electronic chromoendoscopy using narrow-band imaging, flexible spectral imaging color enhancement, and i-scan. Dye-based chromoendoscopy has been demonstrated to improve colorectal dysplasia detection in high-risk patients with long-term inflammatory bowel disease, and electronic chromoendoscopy techniques have been shown to improve characterization of diminutive colorectal lesions, allowing for optical diagnosis during a colonoscopy examination. This article reviews endoscopic imaging using chromoendoscopy techniques for colorectal dysplasia evaluation.

Chromoendoscopy is an image-enhanced endoscopic technique achieved either through dye-based chromoendoscopy, in which topical dyes such as methylene blue or indigo carmine are applied, or electronic chromoendoscopy, which includes optical technologies such as narrow-band imaging (NBI, Olympus), flexible spectral imaging color enhancement (FICE, Fujinon), and i-scan (Pentax).[1,2] Chromoendoscopy provides detailed contrast enhancement of the surface of gastrointestinal mucosa. It can be used during any endoscopic examination to improve detection and characterization of subtle mucosal abnormalities and circumscribed dysplastic lesions in patients with average risk for dysplasia and in patients with increased risk for dysplasia (eg, those with inflammatory bowel disease [IBD], polyposis syndromes). Image-enhancement technologies highlight the subtle appearance of flat colonic adenomas and serrated adenomas, leading to improved detection and characterization.

Colonoscopy, with a 53% reduction of mortality, has become the gold standard screening technique for colorectal cancer prevention.[3,4] In spite of the reduction in mortalities, there is still a 24% miss rate of adenomas, and interval cancers arising from missed lesions are reported.[5-7] Among contributory factors is the lack of full visualization of the mucosa with traditional endoscopic approaches, as these approaches have less sensitivity in detecting conventional adenomas or serrated lesions of a flat or depressed appearance as

opposed to a polypoid appearance. The introduction of high-definition (HD) imaging equipped with an HD monitor and charge-coupled device has led to an overall marginal improvement of detection of adenomas and polyps in patients with average risk undergoing screening colonoscopy.[8,9] The use of HD colonoscopies in patients with IBD resulted in a higher detection of dysplasia compared to standard-definition (SD) colonoscopies.[10] Applying image-enhanced techniques through either dye-based chromoendoscopy or electronic chromoendoscopy with push-button switch technique (ie, NBI, FICE, i-scan) could improve visualization as well as the yield of diagnostic endoscopy in detecting and characterizing dysplastic lesions of subtle, flat, or depressed appearance. This article reviews chromoendoscopy techniques and their role in the detection and characterization of dysplastic lesions in patients with average and increased risks for colorectal dysplasia and neoplasia undergoing screening and surveillance colonoscopies.

Dye-Based Chromoendoscopy

Types of Dye-Based Chromoendoscopy

The stains used for dye-based chromoendoscopy are divided into 2 major categories: absorptive stains, such as methylene blue, and contrast stains, such as indigo carmine. Methylene blue is absorbed by epithelial cells of the small or large intestine, which stain blue as opposed to dysplastic and cancerous lesions, which remain unstained. A topical solution of methylene blue is applied to evaluate dysplastic changes in the esophagus, stomach, small intestine, and large intestine. Methylene blue has also been used to detect colonic neoplasia and to aid in the detection of intraepithelial neoplasia in individuals with ulcerative colitis. Indigo carmine is a dark blue stain that highlights mucosal topography by coating mucosal structures, pits, erosions, and depressions. In the United States, the indigo carmine supply has been temporarily limited due to manufacturing issues and, thus, has not been utilized as frequently as it has been in Europe and Asia.

In general, the application of these agents appears to enhance lesion detection and discrimination by better defining the mucosal surface and light-absorptive patterns. These agents can be applied through nontargeted pancolonic chromoendoscopy (panchromoendoscopy) or targeted chromoendoscopy, which is directed toward visible, subtle abnormalities. Neoplastic and nonneoplastic tissues can be differentiated based upon regular or irregular staining pit patterns, and can subsequently guide targeted biopsies. The staining pit patterns are categorized according to the Kudo pit pattern classification. Kudo and colleagues, in a pioneer study, characterized endoscopic polyp appearance by pit pattern of the colonic mucosa following the application of cresyl violet staining.[11] Specifically, nonneoplastic tissue was defined by rounded or stellar pits, whereas neoplastic tissue was noted to have irregular, tubular, or villous pits.

Technical Aspects of Dye-Based Chromoendoscopy

Recently, major steps have been taken to facilitate the implementation of chromoendoscopy into endoscopic practice, including standardizing traditional techniques of chromoendoscopy (eg, equipment with additional accessories or concentrations of topical solutions) and introducing chromoendoscopy protocols for panchromoendoscopy and targeted chromoendoscopy.[12-16] Kiesslich and colleagues introduced several technical steps known as SURFACE guidelines to facilitate the use of chromoendoscopy during surveillance colonoscopy.[14] These steps include proper bowel preparation, the avoidance of active colitis, the use of an antispasmodic agent, and the ability to identify pit patterns.[14] Optimal bowel preparation is especially necessary for adequate visualization during chromoendoscopy. Lavaging and suctioning of the colon should occur during the insertion phase of the colonoscopy; once the cecum is reached, an endoscopist can apply a dye topically via a spray catheter or water pump system attached to the colonoscope, which enables the endoscopist to spray by pressing a foot pedal.

Panchromoendoscopy utilizes a solution of methylene blue at 0.04% concentration, which is achieved by mixing 10 mL of methylene blue 1% with 240 mL of water. Targeted chromoendoscopy employs a solution of methylene blue at 0.2% concentration, which is achieved by mixing 10 mL of methylene blue with 40 mL of water. A full visualization occurs approximately 1 minute following the application of methylene blue. Dysplastic and inflamed tissues absorb less dye, which allows for different staining features to appear and for better resolution.

Indigo carmine can also be used for panchromoendoscopy, at a 0.03% concentration achieved by mixing 10 mL of indigo carmine 0.8% with 250 mL of water, or for targeted chromoendoscopy, at a more concentrated solution of 0.13% achieved by mixing 5 mL of indigo carmine with 25 mL of water. Indigo carmine coats the mucosal structures through the accumulation of stains into the colonic pits and ridges and allows immediate visualization of subtle changes and lesions.

Safety and Economic Concerns of Dye-Based Chromoendoscopy

Chromoendoscopy is generally considered a safe procedure, and the stains are nontoxic at these minimal concentrations.[1] However, an initial concern was raised after the report of oxidative single DNA damage when methylene blue was used for the evaluation of Barrett

esophagus.[1,17] This risk has not been demonstrated in subsequent clinical trials utilizing a methylene blue agent, and, thus, it has been deemed to be not significant.[1] The current lack of procedure codes for chromoendoscopy as well as a lack of reimbursement for the codes currently in use remain practical challenges to the broad implementation of chromoendoscopy in general endoscopic practice.

Electronic Chromoendoscopy

Electronic chromoendoscopy refers to endoscopic imaging technologies that provide contrast enhancement of the mucosal surface and blood vessels through the application of optical filters and the use of software-based technologies, and include NBI, FICE, and i-scan.

NBI has the potential to improve detection of mucosal abnormalities without the application of staining agents. Although conventional white-light endoscopy (WLE) uses the full visible wavelength range (400-700 nm) to produce a red-green-blue image, NBI illuminates the tissue surface using special filters that narrow the red-green-blue bands and simultaneously increase the relative intensity of the blue band. The resulting narrow-band blue-green light improves visualization of mucosal patterns due to the limited optical scattering and shallow penetration depth; therefore, the color contrast is enhanced between the neoplastic lesions and adjacent normal mucosa. The blue light is also absorbed by hemoglobin for optimal detection of mucosal, glandular, and vascular patterns as well as the presence of abnormal blood vessels that are associated with the development of dysplasia.

Whereas NBI depends upon optical filters within the light source, the FICE system is based on computed spectral estimation technology that processes reflected photons to reconstruct virtual images with a choice of wavelengths. I-scan is a system comparable to FICE; both are based on physical principles similar to NBI but are not dependent upon optical filters. All 3 of these systems lead to enhancement of the tissue microvasculature as a result of the different optical absorption of light by hemoglobin in the mucosa.

The Role of Chromoendoscopy in Patients With Inflammatory Bowel Disease

Patients with IBD have a higher risk for the development of colitis-associated colorectal cancer, which is associated with an increased duration and extent of disease.[18] Colorectal cancer in patients with IBD arises from dysplastic tissue, and IBD-related cancers can develop in the background of chronic inflammation and regeneration.[19-21] The growth pattern of dysplastic tissue is often multifocal and diffuse; thus, its detection may not be optimal with the use of white-light colonoscopy alone. Dysplastic lesions can be challenging to detect due to their subtle, flat nature; their location among inflammatory pseudopolyps; and scarring as a result of postinflammatory mucosal changes.[22-26]

Endoscopic surveillance of dysplasia in patients with ulcerative colitis or Crohn's disease includes random biopsies (≥4 every 10 cm of the colon) and targeted biopsies of any raised or structured areas.[26] Due to the nature of random biopsies, this approach cannot eliminate the possibility of missing lesions. The yield of finding dysplasia in random biopsies taken during HD surveillance colonoscopy examinations has been reported to be 1 in 500 random biopsies.[15,16,27] Furthermore, random biopsies are expensive, labor-intensive, and may distract from careful inspection of the colon. Therefore, chromoendoscopy presents a method of enhancing visualization of subtle lesions and targeted biopsies in the setting of IBD. The main challenge of applying chromoendoscopy in IBD patients remains the level of underlying inflammatory changes, which makes selecting adequate patients with no active disease and following the SURFACE guidelines instrumental.

Dye-Based Chromoendoscopy in Patients With Inflammatory Bowel Disease

The diagnostic yield for detection of dysplasia using dye-based chromoendoscopy has been shown to be higher than SD colonoscopy with random biopsies in patients with long-term IBD undergoing surveillance colonoscopy. Kiesslich and colleagues,[28] in a randomized, controlled study of 263 patients with longstanding ulcerative colitis, evaluated the role of methylene blue panchromoendoscopy with targeted biopsy sampling vs WLE with random biopsy sampling of mucosal inflammation and dysplasia. Panchromoendoscopy resulted in a significant 3.2-fold increase in the number of detected dysplastic lesions compared with WLE. These findings were supported by subsequent trials that confirmed that panchromoendoscopy increased the diagnostic yield of intraepithelial neoplasia when compared with conventional SD colonoscopy and biopsy techniques by a range of 3- to 4.5-fold.[15,16,29,30] Currently, chromoendoscopy with targeted biopsies is the surveillance method recommended by the European Society of Gastrointestinal Endoscopy (ESGE) and the British Society of Gastroenterology (BSG).[31,32] In the United States, chromoendoscopy with HD colonoscopy in patients with long-term IBD has been the suggested method of surveillance introduced by the recent SCENIC (Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations)

international consensus statement and endorsed by the American Society for Gastrointestinal Endoscopy (ASGE) and the American Gastroenterological Association (AGA).[15,16,33] Chromoendoscopy with HD colonoscopy has been primarily utilized in tertiary referral centers, although efforts for its broader implementation have been undertaken.[12] Previous guidelines published by the American College of Gastroenterology (ACG) and the AGA recommend varied approaches for dysplasia surveillance in patients with IBD.[34,35] AGA guidelines recommend that chromoendoscopy be used only by experienced physicians.[34] With the use of enhanced endoscopic techniques, targeted biopsies of suspicious lesions may be performed as an alternative to random biopsies.[34] By contrast, the guidelines provided by the ACG do not recommend routine use of chromoendoscopy-enhanced surveillance colonoscopy in low-risk patients.[35]

The SCENIC consensus statement provides a summary of the available data for the management of dysplasia and its surveillance in patients with IBD.[15,16] Additionally, it addresses how to perform surveillance colonoscopy for the detection of dysplasia and how to describe and manage visualized dysplasia. The SCENIC consensus statement introduced a new set of terms to describe dysplasia and replaced confusing terms for colorectal dysplasia in IBD, such as dysplasia-associated lesion mass and adenoma-like mass. Lesions and their features are now described according to the new SCENIC classification system and are divided into polypoid or nonpolypoid lesions (Table, Figures 1 and 2). Decisions regarding endoscopic resection or surgical management of the lesion are made based upon these endoscopic features.

The SCENIC consensus statement conditionally recommends (with low-quality evidence) chromoendoscopy over HD white-light colonoscopy alone for dysplasia detection in IBD based on results from a study by the Mayo Clinic.[15,16,36] A recent prospective, parallel-group, randomized study demonstrated that HD chromoendoscopy leads to better detection of dysplastic lesions compared to HD-WLE alone (22.0% vs 9.5%; *P*=.04).[37]

The advantage of using chromoendoscopy in IBD patients has been suggested in subsequent studies. Marion and colleagues evaluated 68 patients with ulcerative colitis within a 5-year period using random biopsy, WLE, and chromoendoscopy.[38] Overall, 6 dysplastic lesions were detected by random biopsy specimens, 11 by WLE, and 27 by chromoendoscopy. However, no clear distinction was made between the use of SD and HD colonoscopies in the final analysis.[38] Gasia and colleagues reported a cohort of 454 IBD patients undergoing surveillance between 2011 and 2014, with a total of 243 lesions detected.[39] All dysplastic lesions were detected in similar proportions of patients by HD colonoscopy and by chromoendoscopy using a targeted-biopsy approach. No dysplasia was seen from random biopsies. A collection of targeted biopsy specimens appeared to be sufficient for detecting colonic neoplasia in patients undergoing HD colonoscopy or chromoendoscopy.[39]

A prospective, multicenter trial from Spain confirmed the value of dye-based chromoendoscopy in 350 IBD patients undergoing surveillance colonoscopy under real-life conditions with a white-light colonoscopy assessment followed by indigo carmine chromoendoscopy examination in segmental fashion.[40] Results showed a 57% incremental yield for IBD-associated neoplasia using dye-based chromoendoscopy vs white-light colonoscopy alone. A total of 94 (15.7%) dysplastic (1 cancer, 5 high-grade dysplasia, 88 low-grade dysplasia) and 503 (84.3%) nondysplastic lesions were detected. Colonoscopies were performed with either SD (41.5%) or HD (58.5%). An overall incremental detection yield for dysplasia was comparable between SD chromoendoscopy and HD chromoendoscopy (51.5% vs 52.3%; *P*=.30). Furthermore, sensitivity, specificity, positive predictive value, and

Table. SCENIC Classification for IBD-Related Colorectal Neoplasia Using Modified Paris Classification[15,16]

Visible Dysplasia (>90%) *Dysplasia identified on targeted biopsies from a lesion detected at colonoscopy*
Polypoid Neoplasia *Lesion protruding from the mucosa into the lumen ≥2.5 mm* - Sessile: lesion not attached to mucosa by a stalk - Pedunculated: lesion attached to the mucosa by a stalk
Nonpolypoid Neoplasia *Lesion with little (<2.5 mm) or no protrusion above the mucosa* - Slightly elevated: lesion with protrusion but <2.5 mm above the lumen - Flat: lesion without protrusion above the mucosa - Depressed: lesion with at least a portion depressed below the level of mucosa
Descriptors - Ulcerated: ulceration present within the lesion - Distinct border: lesion border is discrete and distinguished from surrounding mucosa - Indistinct border: lesion border is not discrete and cannot be distinguished from surrounding mucosa
Invisible Dysplasia (<10%) *Dysplasia identified on random (nontargeted) biopsies of colonic mucosa without visible lesions*

IBD, inflammatory bowel disease; SCENIC, Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations.

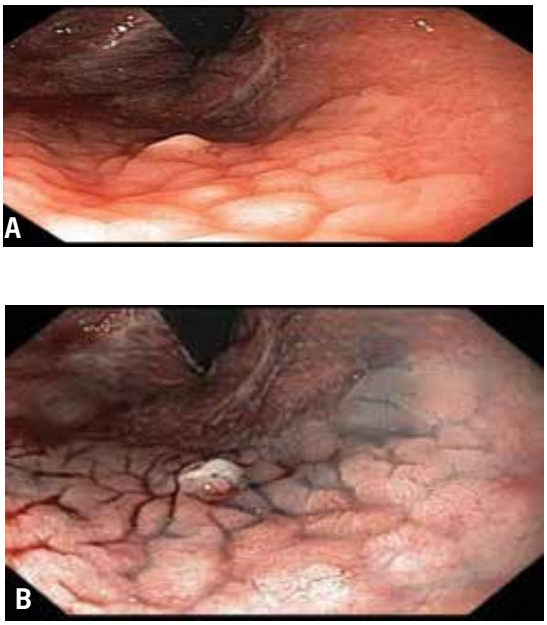

Figure 1. High-definition white-light endoscopy (**A**) and chromoendoscopy (**B**) images of low-grade polypoid dysplastic lesions in a patient with inflammatory bowel disease.

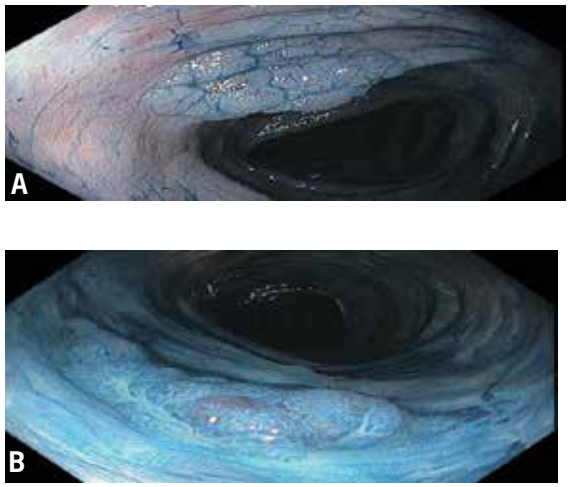

Figure 2. High-definition dye-based chromoendoscopy (**A**) and narrow-band imaging chromoendoscopy (**B**) images demonstrating a low-grade polypoid dysplastic lesion in a patient with inflammatory bowel disease.

negative predictive value (NPV) for optical diagnosis of dysplasia were 70%, 90%, 58%, and 94%, respectively. Endoscopic features predictive of dysplasia included proximal location, loss of innominate lines, polypoid morphology, and Kudo pit pattern Types III to V. Thus, it appears that dye-based chromoendoscopy has a high diagnostic yield for dysplasia detection in IBD patients, irrespective of the type of technology employed. In vivo, chromoendoscopic, optical diagnosis is highly accurate for ruling out dysplasia, especially for experienced physicians. Lesion characteristics can aid an endoscopist with in situ therapeutic decisions.

In the United States, chromoendoscopy with targeted biopsies remains the preferred method for dysplasia surveillance and is performed primarily in tertiary academic centers by trained endoscopists for high-risk patients with IBD, including long-term IBD and prior history of severe colitis requiring escalation therapy, dysplasia, or primary sclerosing cholangitis.[15,16,33] However, random biopsies plus targeted biopsies remain an alternative when chromoendoscopy is not available or optimal (eg, poor bowel preparation, presence of pseudopolyps, active inflammation). Further studies are needed to address reimbursement issues and training processes prior to the broad implementation of chromoendoscopy in routine clinical practice in the United States.

In contrast, panchromoendoscopy with targeted biopsy for neoplasia surveillance in patients with longstanding IBD has been strongly recommended by the ESGE and the BSG.[31,32] According to recent ESGE guidelines, the routine use of 0.1% of methylene blue or 0.1% to 0.5% of indigo carmine during panchromoendoscopy with targeted biopsies is recommended for dysplasia surveillance in patients with longstanding IBD.[32] Furthermore, under certain circumstances (eg, quiescent disease activity, adequate bowel preparation), nontargeted 4-quadrant biopsies may not be required.

Electronic Chromoendoscopy in Patients With Inflammatory Bowel Disease

Studies have not demonstrated an improved detection rate of dysplasia from NBI vs SD or HD colonoscopies.[41-43] Pellise and colleagues compared HD colonoscopy plus NBI with HD colonoscopy plus dye-based chromoendoscopy, and also demonstrated no difference in the detection rates of dysplasia among these 2 groups, although a higher miss rate of dysplastic lesions occurred in the HD colonoscopy plus NBI cohort compared to HD colonoscopy plus dye-based chromoendoscopy.[44] A prospective, multicenter, tandem colonoscopy study by Leifeld and colleagues[45] compared neoplasia detection rates of NBI and white-light colonoscopy in 159 patients with longstanding ulcerative colitis undergoing surveillance. A total of 54 dysplastic lesions were detected in 36 (23%) patients, with 30 lesions detected by WLE and 31 detected by NBI. It was notable that NBI appeared to miss more nonadenomatous lesions (17/26), while white-light colonoscopy missed more adenomatous lesions (15/24).

In summary, NBI has not been demonstrated to improve detection rates of dysplastic lesions when

compared with white-light colonoscopy, and there are no available studies evaluating the role of other electronic chromoendoscopy techniques, such as FICE and i-scan, in IBD patients.

The Role of Chromoendoscopy in Polyp Characterization and Histology Prediction

Chromoendoscopy appears to be a promising technique for the characterization and real-time prediction of lesion histology, known as a virtual or optical biopsy, and its use in discriminating neoplastic from nonneoplastic polyps has been studied extensively.[46] As specified in guidelines from the ASGE, a polyp can be left in situ instead of being sent to pathology to be characterized, resected, and discarded if the technology has high accuracy and a high NPV (>90%).[47] Thus, chromoendoscopy has been evaluated as a potential tool in a characterize-resect-and-discard approach, in which the histologic diagnosis is based solely on the endoscopic image with photographic confirmation. This approach may further allow directing biopsies only to neoplastic lesions while forgoing pathologic assessment of diminutive polyps, carrying significant cost savings potential. Based on a study by Hassan and colleagues, an estimated $33 million may be saved annually using the characterize-resect-and-discard approach.[48] Furthermore, the annual upfront cost savings created by forgoing pathologic assessment of diminutive polyps was calculated to exceed $1 billion.[49]

Dye-Based Chromoendoscopy and Polyps

Dye-based chromoendoscopy can highlight different patterns on the surface of colonic polyps known as pit patterns. These specific patterns were introduced by Kudo and colleagues using magnifying endoscopy and can reliably predict the histology of polyps.[11,50] The Kudo pit pattern classification for colonic lesions has become widely used to define colonic lesions.[11] Type I (round pits) and Type II (stellate pits) represent nonneoplastic lesions, whereas Type III (tubular pits), Type IV (gyros-like pits), and Type V (irregular pits) correspond to neoplastic lesions. A meta-analysis[51] and systematic review[52] compared chromoendoscopy with conventional endoscopy and confirmed a sensitivity of 92% vs 94%, respectively, and a specificity of 82% vs 85%, respectively, in predicting neoplasia vs nonneoplasia using Kudo pit pattern classification. Fu and colleagues[53] demonstrated the highest accuracy for predicting neoplasia vs nonneoplasia when using HD chromoendoscopy followed by SD chromoendoscopy and conventional colonoscopic evaluation. Furthermore, dye-based chromoendoscopy was determined to be more accurate for histology prediction of larger polyps as opposed to diminutive polyps.[54,55]

Electronic Chromoendoscopy and Polyps

Electronic chromoendoscopy has also been shown to be a promising tool in the characterization of colorectal lesions, including predicting histology of neoplastic vs nonneoplastic lesions. It can be applied particularly for evaluation of diminutive polyps, potentially limiting unnecessary resection or pathologic evaluation of small polyps. The concept of electronic chromoendoscopy serving as an optical biopsy for polyps may allow for a predict-resect-and-discard approach for diminutive polyp management, as suggested by the ASGE statement.[56]

Narrow-Band Imaging A systematic review by van den Broek and colleagues[52] summarized data on the performance and clinical utility of NBI during colonoscopy. Although NBI did not demonstrate a significant improvement in adenoma detection, the data confirmed the value of NBI in differentiating neoplastic from nonneoplastic colorectal polyps when used by trained endoscopists. The main advantage of NBI appears to be characterization, as the technique has a relatively high sensitivity (90%-95%) and specificity (80%-85%) for differentiating neoplastic from nonneoplastic lesions.[57] This level of accuracy is comparable to the accuracy of the dye-based chromoendoscopy approach, based on available studies by experts in endoscopic imaging.[58,59] Several studies examined the role of NBI for colorectal polyp differentiation.[60-68] NBI was shown to be able to differentiate neoplastic from nonneoplastic polyps based on Kudo pit patterns in initial studies and on surface vascular patterns in subsequent studies, with a sensitivity and specificity of 91% and 89%, respectively, which is comparable to dye-based chromoendoscopy.[60,63,67,68]

Recent trials confirmed a high accuracy of NBI for the diagnosis of small colorectal lesions (<10 mm) in select cases of high-quality and high-confidence images interpreted offline.[63,67] Rex[63] acknowledged the limitations of electronic magnification in visual assessment and, thus, introduced the concept of confidence levels to the endoscopic interpretation of colorectal polyp histology. A high confidence level is defined by clinical judgment to make a diagnosis with sufficient certainty such that histologic confirmation is not necessary.[63] Based on that study, predictions of the histology of diminutive hyperplastic and adenomatous polyps were made with high confidence (81% and 92%, respectively). High confidence allowed sufficient accuracy (>91%) for the use of NBI in the identification of distal hyperplastic polyps that do not need resection, as well as for postpolypectomy surveillance without pathologic evaluation of polyps 5 mm in size or smaller.[63]

Ignjatovic and colleagues demonstrated that for polyps less than 10 mm in size, in vivo optical diagnosis

using NBI as virtual chromoendoscopy or, in a few cases, dye-based chromoendoscopy can represent an acceptable approach for polyp characterization.[67] Wada and colleagues reported that both NBI and chromoendoscopy can be useful in distinguishing neoplastic from nonneoplastic colorectal lesions based on pit pattern and vascular pattern analyses.[69] Rastogi and colleagues also showed that with a simple classification of surface mucosal and vascular patterns, NBI without magnification was highly accurate and significantly superior to HD white-light imaging for prediction of adenomas.[60] Wu and colleagues estimated the overall sensitivity of NBI in diagnosing adenomatous polyps to be 92% while specificity was 83%, with similar sensitivities and specificities for the use of NBI with and without magnifications.[70] Thus, the general conclusion has been that NBI with or without magnification is adequate in identifying adenomas vs nonadenomas, especially when high confidence is applied.

The NBI International Colorectal Endoscopic (NICE) Classification using NBI without magnification has been useful for characterizing polyps, allowing for accurate assessment based on the surface color and vessel surface structure of diminutive colorectal polyps, with a high sensitivity and NPV of greater than 90%.[71]

Kaltenbach and colleagues[72] confirmed that real-time optical diagnosis using NBI colonoscopy may replace pathologic diagnosis for the majority of diminutive colorectal polyps. Using colonoscopy with near-focus view increased the confidence of the optical diagnosis when compared to the standard view (85.1% vs 72.6%). Overall, 75.3% of polyps had a high-confidence, accurate prediction using near focus compared with 63.1% using standard view. Alternatively, Wallace and colleagues demonstrated that both traditional and new dual-focus colonoscopies provide highly accurate optical polyp discrimination, and no differences were found between the 2 systems in terms of lesion detection and characterization.[73]

A meta-analysis of 28 studies by McGill and colleagues confirmed that NBI can accurately differentiate neoplastic from nonneoplastic lesions with high sensitivity and a NPV greater than 90%, thus meeting preservation and incorporation of valuable endoscopic innovations (PIVI) criteria.[74] Furthermore, recent studies demonstrated that a high-confidence optical biopsy for lesions less than 6 mm meets the PIVI sensitivity threshold and leads to adequate surveillance interval recommendations in more than 90% of patients.[72,73,75] Additionally, virtual chromoendoscopy with NBI assessment has been demonstrated as part of a standardized imaging protocol in detecting dysplasia recurrence after endoscopic mucosal resection (EMR) of large, laterally spreading lesions in the colon.[76] Desomer and colleagues[76] confirmed that NBI detects more flat dysplastic lesions than white-light HD colonoscopy for the evaluation of scars post-EMR.[76] This standardized approach using NBI examination may improve targeting biopsies and avoid inadequate sampling, therefore increasing diagnostic yield in assessing post-EMR scars.

I-scan I-scan has been shown to predict histology with acceptable accuracy, sensitivity, and specificity of 86%, 98%, and 93%, respectively.[77,78] No significant difference between NBI and i-scan has been reported (accuracy, 87.8% vs 90.7%).[79] A study by Basford and colleagues demonstrated high accuracy and a high NPV for i-scan HD and HD alone in characterizing small polyps.[80]

Flexible Spectral Imaging Color Enhancement FICE was adequate in distinguishing neoplastic from nonneoplastic colorectal lesions, with a reported sensitivity of 93% and NPV of 85%.[81] When analyzing diminutive colorectal lesions, FICE and dye-based chromoendoscopy were comparable in the prediction of neoplastic vs nonneoplastic lesions.[82]

A study by Repici and colleagues[83] assessed the accuracy and reliability of histologic prediction of polyps smaller than 1 cm by applying the NICE Classification to the FICE system. The study confirmed an overall suboptimal accuracy of 77% and a NPV of 88%; a high confidence of diagnosis was reached in only 68.5% of cases.[83] These results suggest caution when applying the NICE Classification to other technological tools. Further studies on FICE are suggested given that newer, high-resolution FICE systems provide better contrast for vascular and surface patterns than older FICE systems.

Virtual Chromoendoscopy Virtual chromoendoscopy has been shown to be able to accurately distinguish neoplastic lesions from nonneoplastic lesions. A meta-analysis by Wanders and colleagues confirmed that an adequate optical diagnosis could be achieved with NBI, i-scan, and FICE.[84] Although studies performed in academic centers by experienced endoscopists on the performance of virtual chromoendoscopy for the optical diagnosis of adenomatous and nonadenomatous polyps are encouraging, community-based studies are reporting overall subpar results in which the PIVI criteria of NPVs greater than 90% are not met.[85,86] It is anticipated that with appropriate training, NBI with other electronic chromoendoscopy techniques will be used routinely for better lesion discrimination and characterization, and will allow for the adoption of the characterize-resect-and-discard approach outlined in the ASGE guidelines. A 2016 study by Patel and colleagues[87] investigated whether endoscopists without prior training in NBI could achieve the thresholds recommended by the ASGE. High confidence characterization was the strongest

predictor of accuracy at 94.7%, followed by surveillance agreement at 91.2%. Overall surveillance interval prediction of 97% would lead to surveillance colonoscopy on time or earlier, and performance improved with time. However, it was noted that most endoscopists would require auditing of performance in time, as only 27% of participants recognized adenomatous lesions with adequate sensitivity.[87] Thus, although numerous studies have demonstrated that trained endoscopists have met ASGE benchmarks, additional studies among general endoscopists with no prior NBI training are still needed.[46] Furthermore, the question remains whether high-magnifying endoscopy would improve the rates of high-confidence, NBI-based optical diagnosis without magnification for differentiating neoplastic from nonneoplastic colorectal lesions among general endoscopists. A study by Iwatate and colleagues[88] demonstrated that the rates of high-confidence optical diagnosis using NBI with magnification were significantly higher than those of NBI without magnification for diminutive polyps (92.9% vs 79.5%) and small polyps (94.7% vs 84.2%; *P*=.048). Interestingly, for diminutive polyps, only experienced endoscopists achieved the ASGE-recommended threshold levels for accuracy and NPVs. It is important to note that this high-magnification function is only used in systems in Japan and the United Kingdom, and optical high magnification has not been used in the United States. While computer-training modules appear to improve performances, the ideal training has yet to be determined based upon expert panel recommendations.[46]

The Role of Chromoendoscopy in Patients With Hereditary Syndromes

Chromoendoscopy can benefit patients at high risk for colorectal cancer, including patients with Lynch syndrome or serrated polyposis syndrome, as the potential to improve lesion characterization and detection reduces the risk of interval cancers. Based on small, tandem colonoscopy studies, higher rates of adenomas or polyps have been detected in patients with Lynch syndrome via conventional dye-based chromoendoscopy compared to SD- or HD-WLE.[89-92] The role of electronic chromoendoscopy in patients with Lynch syndrome was also evaluated in prospective cohort studies.[91,93] East and colleagues demonstrated that an additional pass with NBI vs a single pass with HD-WLE increased the detection of adenomas (absolute difference, 15%; 95% CI, 4%-25%).[93] Hüneburg and colleagues[91] reported that the total number of flat adenomas detected by a second pass with dye-based chromoendoscopy was higher when using only HD-NBI during the first pass. A 2017 study by Bisschops and colleagues[94] noted that virtual chromoendoscopy with i-scan reduces the adenoma and polyp miss rate in patients with Lynch syndrome independently of inspection time. In this tandem, randomized, controlled, crossover trial, the adenoma miss rate was significantly higher for HD-WLE (62%) compared with i-scan (12%; relative risk, 0.44; 95% CI, 0.21-0.87; *P*=.007).[94] The current recommendation endorsed by the ESGE is to routinely use HD pan-chromoendoscopy in patients with known or suspected Lynch syndrome (via conventional chromoendoscopy, NBI, or i-scan) or serrated polyposis (via conventional chromoendoscopy or NBI), although overall evidence remains of low quality due to limited studies.[32]

The Role of Chromoendoscopy in Adenoma Detection in Patients With Average Risk

Dye-Based Chromoendoscopy and Adenoma Detection

The main advantages of dye-based chromoendoscopy techniques appear to be the detection of small and flat lesions missed via conventional colonoscopy, and the ability to distinguish neoplastic from nonneoplastic lesions during ongoing colonoscopy.[55,95-100] Three randomized, controlled trials compared dye-based panchromoendoscopy with conventional SD colonoscopy; only 1 confirmed a significant increase in the detection of small adenomas at the disadvantages of longer withdrawal time and procedure time.[97,99,101] In a tandem study,[100] a second chromocolonoscopy increased detection of additional adenomas, but the difference was not significant. A Cochrane review comparing dye-based chromoendoscopy to conventional endoscopy for the detection of colorectal polyps revealed that dye-based chromoendoscopy is likely to yield more patients with at least 1 neoplastic lesion and significantly more with 3 or more neoplastic lesions.[51,100] In these studies, all enrolled patients were considered to be at high risk for colorectal cancer. In a study of average-risk patients, HD dye-based chromoendoscopy marginally increased overall adenoma detection and yielded only a modest increase in flat and small adenoma detection when compared to HD white-light colonoscopy.[102] Therefore, these findings do not support the routine use of HD chromoendoscopy for colorectal cancer screening in average-risk patients.[103] Alternatively, targeted dye-based chromoendoscopy has been demonstrated to be beneficial in the characterization of flat and depressed colorectal lesions.[96]

In summary, dye-based chromoendoscopy is known to achieve only marginally higher adenoma detection rates vs SD or HD colonoscopy, and specific benefits are directed toward diminutive, flat, and serrated lesions.

Electronic Chromoendoscopy and Adenoma Detection

NBI may be a useful tool in the detection of colorectal lesions.[104,105] However, numerous randomized studies

demonstrated no overall improvement of adenoma detection rates.[52,64,106] In a study of 401 patients randomized to undergo either NBI colonoscopy or SD colonoscopy, a higher adenoma detection rate was demonstrated in the NBI colonoscopy group compared to the SD colonoscopy group (23% vs 17%) in the initial phase of the study, suggesting that exposure to NBI leads to increased adenoma detection with both conventional and image-enhanced methods.[107] A study by Rex and Helbig[64] included 434 patients undergoing colonoscopy examinations with either HD-NBI or white-light HD colonoscopies and found no difference in detection between the imaging techniques. However, the adenoma detection rate was nearly doubled compared to well-documented historical controls, suggesting a benefit primarily from HD colonoscopy.[64] Results of another prospective, randomized, back-to-back trial comparing NBI to conventional colonoscopy for adenoma detection found that the miss rate for polyps and adenomas is lower with HD-NBI than with conventional colonoscopy.[108]

A Cochrane meta-analysis compared polyp detection using NBI with SD- and HD-WLE either together or separately.[109] Study results demonstrated no statistically significant difference between white-light imaging (SD or HD) and NBI in the detection of patients with colorectal polyps. Specifically, NBI compared to HD white-light imaging was not significantly different in detecting adenomas and polyps. These results were similar to those from additional meta-analyses.[110-112]

The FICE system has been evaluated for use in the detection of colorectal lesions.[113-115] When FICE was compared with SD-WLE or with targeted chromoendoscopy, there was no improvement of adenoma detection rates.[113] A large, randomized trial by Aminalai and colleagues[116] demonstrated no advantage of the FICE technique over conventional HD endoscopy. Both the screening and the diagnostic colonoscopy subgroups had a similar overall adenoma detection rate (0.28 in both groups), total number of adenomas (184 vs 183), and detection of subgroups of adenomas.[116] In another prospective, randomized trial of tandem colonoscopy, no objective advantage was found between the FICE technique and conventional high-resolution endoscopy in terms of improved adenoma detection rate.[117] The adenoma miss rate with FICE showed no significant difference when compared with that of WLE (6.6% vs 8.3%; P=.59).[117]

In a prospective, randomized trial, Pohl and colleagues[62] compared the FICE technique with other modalities such as standard colonoscopy and conventional chromoendoscopy with indigo carmine in low- and high-magnification modes for the determination of colonic lesion histology. In this study, the FICE system was able to identify morphologic details that efficiently predict adenomatous histology, was superior to standard colonoscopy, and was equivalent to conventional chromoendoscopy. Hoffman and colleagues[78,118] demonstrated that HD endoscopy combined with the i-scan system is significantly superior in detecting colorectal neoplasia compared with standard video colonoscopy, and it allows for the prediction of histology of the identified lesions and surface enhancement. Additionally, HD colonoscopy with i-scan identified significantly more patients with at least 1 neoplasm compared with standard resolution endoscopy (38% vs 13%; P<.001). However, given the poor results for improved adenoma detection using NBI and FICE and the low level of adenoma detection in the control arm of the i-scan study (13%), additional studies are needed to determine whether i-scan improves adenoma detection and to evaluate the final application (including efficacy and cost-effectiveness) of FICE, NBI, and i-scan in routine endoscopy practice.

Summary

Dye-based chromoendoscopy techniques have been shown to be especially beneficial in patients with increased risks for colorectal neoplasia, such as IBD. European guidelines, including the BSG and the ESGE, recommend chromoendoscopy with targeted biopsies as the procedure of choice. The ASGE and the AGA society guidelines do not universally recommend the broad application of chromoendoscopy, although both societies endorse the recent SCENIC consensus statement and recognize chromoendoscopy as a reasonable alternative to standard colonoscopy with random biopsies for IBD surveillance with appropriately trained endoscopists. The ACG recognizes that chromoendoscopy may be particularly important in IBD patients at high risk for cancer (eg, history of prior dysplasia, primary sclerosing cholangitis) but not in IBD patients at low risk.

Electronic chromoendoscopy has been demonstrated to be highly accurate for the characterization of diminutive polyps as neoplastic or nonneoplastic by experienced endoscopists, and has met the ASGE's PIVI criteria of greater than 90% accuracy for characterization. However, it remains to be seen whether this high level of accuracy can be achieved by general endoscopists. Expert panels recommend that any electronic chromoendoscopy technique such as NBI, FICE, or i-scan should be used only after demonstrating its competency.[46] Currently in the United States, both dye-based and electronic chromoendoscopy are the preferred methods used primarily in tertiary academic centers by expert endoscopists in high-risk patients for dysplasia detection and characterization as well as diminutive polyp management. In Europe, chromoendoscopy is recommended for routine use by

all endoscopists in patients with long-term IBD or with hereditary polyposis syndromes.

A significant limitation of all advanced imaging studies is that they were performed by experienced endoscopists. Although the results are promising overall, chromoendoscopy technologies should be universally demonstrated to be highly accurate in general community practices prior to their broad implementation. Additionally, the cost of the technologies, reimbursement, and adequate training remain important concerns and should be further explored.

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