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INFLAMMATORY BOWEL DISEASE

Artificial Intelligence and Enhanced Colonoscopic Imaging Surveillance for Inflammatory Bowel Disease: Beyond Random Biopsies

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Abstract

Inflammatory bowel disease confers an increased risk for colorectal cancer among individuals with long standing colonic disease. Current guidelines for optimal management of these patients recommend high quality surveillance colonoscopies every 1-2 years, performed during times of quiescent disease. In many instances, dysplastic changes can be difficult to visualize endoscopically in these patients. Accordingly, there has been increasing use of endoscopic advances to assist in the diagnosis and management of dysplasia. These include high-definition endoscopes, chromoendoscopy, and narrow band-imaging. There is increased evidence additionally, that with these advanced imaging modalities early recognition of dysplastic lesions is enhanced. The emerging standard of care is for patients with colonic dysplasia to be evaluated for endoscopic mucosal resection and, if appropriate, referral to experts in the technique, thereby decreasing or avoiding the need for surgical resection. This approach is now recognized as a safe and effective risk reduction for colorectal cancer. Future advances also highlight promising results for artificial intelligence systems in polyp detection and characterization, for which there is already an FDA approved device available in the United States.

Introduction

Inflammatory Bowel Disease (IBD), comprised of ulcerative colitis (UC) and Crohn's disease (CD), is a well-known chronic inflammatory disease of the digestive tract with a number of long-term consequences resulting from inflammation. Chief among these long-term complications is an increased risk for colorectal cancer (CRC), which was described as early as 1925 by Crohn and Rosenberg [1]. Current population-based estimates suggest an overall CRC incidence of 5% at 20 years following the initial onset of disease [2]. The clinical implications of CRC in IBD remain significant, as CRC may account for up to 15% of deaths among IBD patients [3]. Due to this underlying risk, current GI society recommendations advocate for dysplasia surveillance every one to two years starting after 8 years of disease in UC or CD with greater than one-third colonic involvement [2,4,5].

This chapter seeks to review the current evidence related to endoscopic technologies for the enhanced detection and treatment of dysplasia in IBD. Much of this is an in-depth review and discussion of the findings from the SCENIC consensus (Surveillance for Colorectal Endoscopic Neoplasia Detection and

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Management in Inflammatory Bowel Disease Patients), which remains the guiding literature on the surveillance and management of dysplasia in IBD [5]. Additionally, we discuss the emerging role of artificial intelligence (AI) and the potential applications of this technology toward increasing the quality of care for IBD patients.

Epidemiology and pathogenesis of CRC in IBD

Unfortunately, the true incidence and prevalence of CRC among persons with IBD is unknown, due reliance on retrospective data that may not entirely reflect the continued advances in treatment and screening, much less the variance in expertise of the care providers, all of which can affect the incidence reports. There is relative consensus as to the risk factors among which the major risks include longer duration of disease, increased inflammatory activity, younger age of diagnosis, greater extent of colonic inflammation, coexisting primary sclerosing cholangitis (PSC), and family history of a first degree relative with CRC [2].

With respect to the incidence and prevalence of CRC among IBD patients, the literature has shown this to be a moving target, including analysis of outcomes from cancer prevention and screening programs. A single-center study from 2006 reviewed 30 years of surveillance colonoscopies comprising 5932 years of patient follow up found a cumulative incidence of 2.5%, 7.6%, and 10.8% at 20, 30, and 40 years respectively [6]. Concerningly, among incident cancers, 16 of 30 were found to be interval cancers despite ongoing surveillance [6].

An early, often-cited, meta-analysis from 2001 estimated for any patient with UC (irrespective of disease extent) the CRC prevalence to be 3.7% with incidence rate of 2% at 10 years, 8% at 20 years, and 18% at 30 years [7]. Of note, this meta-analysis included review of 196 studies dating back to 1925, and all studies included were before the advent of biologic therapies or high-definition endoscopy. Other confounding factors which have been identified include the impact of population-based increases in CRC screening and better recognition of possible lead-time bias with improved detection of dysplastic lesions due to advances in technology.

Recognizing that treatment may alter the inherent CRC risk, a better estimate comes from data out of the prospective observation French cohort study group, CESAME, which was designed to assess the risks of any cancer or high-grade dysplasia (HGD) in IBD patients, along with the impact of immunosuppressive therapy (thiopurines and anti-TNF) on these risks [8]. Results of this cohort suggest that there is an increased risk for patients with IBD with an overall standardized incidence of 2.2 (95% CI 0.1-0.9, p =0.03); however, this cohort study also identified that the risk is divergent between those with long-standing extensive colitis (standardized incidence ratio 7.0, p<0.001) versus those without (standardized incidence ratio 1.0, p=0.84) [8]. Furthermore the adjusted HR was significantly decreased at 0.28 (p=0.03) for those who had received prior thiopurine, suggesting immunosuppression is able to modify underlying risk of CRC.

More recently, a meta-analysis evaluated the risk of CRC in IBD, using only population based-cohort studies, to address reports of declining rates of CRC in the general population and IBD patients [9]. A cumulative risk of CRC was 1%, 2%, and 5%, after 5, 10, and 20 years of disease duration, respectively [9]. These results most closely represent the opinion of key experts who have agreed that long-standing IBD remains a risk factor for IBD. The reasonable most current estimate is a 5% incidence after 20 years of disease, with the acknowledgement that large-scale and high quality trials are needed for confirmation [10].

Colonoscopic surveillance

As previously noted, the SCENIC international consensus published jointly by the American Gastroenterological Association (AGA) and American Society for Gastrointestinal Endoscopy in 2015 was a multidisciplinary group of global IBD experts who reviewed the existing literature on the surveillance and management of dysplasia in IBD. When possible, GRADE methodology was utilized to provide strength for the expert recommendations [11]. This consensus statement remains the primary guidance for practicing clinicians on how to approach dysplasia surveillance in IBD patients. This section will aim to provide a summary of the SCENIC consensus recommendations stratified by type of endoscopic technology, while supplementing with more recent articles and updated guidelines.

Finally, although this section is focused on technological advancements to assist in colonoscopy, paramount to a successful surveillance examination. This is performed during periods of quiescent inflammation/well-controlled disease, additionally with both a high quality colonoscopist and bowel preparation. For the latter, only excellent screening should be considered "adequate" and we advocate strongly for the use of the Boston Bowel Prep scale. Recent evidence supports this scale as the new "gold standard" for documenting bowel preparation, not only as a validated screening tool with near perfect inter-rater reliability and substantial intra-rater reliability, but also excellent correlation with polyp detection and recommended screening intervals for repeat colonoscopy [12]. Evidence from studies on colorectal screening in the general population shows that intermediate quality preparation compared to high-quality preparation is associated with a significant decrease the detection of sessile serrated lesions for both the entire (4.6% *vs* 12%, OR 0.37, 95% CI 0.15-0.97) and right colon (1.5% *vs* 7.9%, OR 0.19, 95% CI 0.05-0.81), which correlates to both a total BBPS score <7 (4.7% *vs* 12.6%, OR 0.36, 95% CI 0.19-0.67) and any BPPS segment score of 2 compared to 3 (4.7% vs 9.5%, OR 0.50, 95% CI 0.26-0.94) [13].

Definition of terms

Standard Definition (SD) endoscopes use charge-coupled device chips to provide image quality ranging from 100,000-400,000 pixels, which is similar to old cathode ray televisions with 300,000 pixels [14]. *High definition (HD*) endoscopes provide significantly improved image resolution at least 850,000 pixels, although some systems exceed 2 million pixels [14]. Certain HD endoscopes are also capable of high-magnification through the use of a movable lens for optical zoom in addition to digital zoom through the endoscopic processors, allowing total zoom up to 150 times compared to 30 times with a conventional endoscope [14]. Both SD and HD endoscopes utilize White Light (WL) endoscopy and are sometimes further abbreviated as SDWL or HDWL.

Chromoendoscopy (CE) is a specialized endoscopic technique also known as "dye-based image enhanced endoscopy" in which contrast enhancing dye is instilled through either the colonoscope working channel or water jet channel to provide enhanced mucosal visualization. For IBD surveillance, methylene blue and indigo carmine are the primary dyes utilized. Methylene blue is an absorptive dye taken up absorbing intesti-

nal epithelial cells, whereas indigo carmine is a non-absorptive dye that pools in crevices of mucosal surface to accentuate the border and surface topography of lesions [15]. Chromoendoscopy results in improved differentiation between neoplastic and nonneoplastic lesions with a reported sensitivity and specificity of 93% [16]. Early studies with CE demonstrated increased detection of dysplastic lesions in IBD surveillance such that multiple societies recommended adoption of the technique as early as 2005 for the Crohn's and Colitis Foundation of America (CCFA) and 2010 for the AGA [17,18].

Narrow Band Imaging (NBI) is a specialized light filter available on certain endoscopes which filters light to narrow bandwidths of blue (415nm) or green (540nm) which are the optimal wavelengths for absorption by hemoglobin. Thus, NBI leads to enhancement of the mucosal surface vessels pattern which can be categorized according to the NBI International Colorectal Endoscopic (NICE) classification for determination of polyp histology [19]. Specifically, NBI related to imaging technology for Olympus (Tokyo, Japan), whereas *i*-scan and Fuji Intelligent Chromo Endoscopy are the trade names for Pentax (Tokyo, Japan) and Fujinon (Tokyo, Japan) scopes, respectively [20].

Comparison of technologies

Standard definition *vs* high definition

The SCENIC consensus offers a strong recommendation with 80% agreement that when performing white-light colonoscopy, high definition is recommended over standard definition [5]. This is based on a single retrospective study of 353 patients which found a prevalence ratio of 2.3 (95% CI, 1.03-5.11) for the detection of dysplasia or cancer, in addition to significantly more endoscopically detected dysplasia (versus invisible dysplasia) with a risk ratio of 3.4 (95% CI, 1.3-8.9) [21]. Arguably, the distinction of standard definition versus high definition endoscopes has become a moot point given that modern endoscopes now incorporate HD technology and standard definition scopes are being phased out as practices replace their aging technology.

Standard definition *vs* chromoendoscopy

The SCENIC consensus offers a strong recommendation with 85% agreement that when performing standard definition colonoscopy, chromoendoscopy is recommended over standard white light colonoscopy [5].

Eight studies comparing chromoendoscopy to SDWL colonoscopy noted a trend towards increased dysplasia detection with an absolute risk increase ranging from 0-10%, however none of these studies achieved statistical significance [5]. The SCENIC authors completed a meta-analysis of these studies and subsequently found a significant increase in dysplasia detection with a RR 1.8 (95% CI 1.2-2.6) and absolute increase of 6% (95% CI 3-9 %) [5].

While total procedural time was increased by an average of 10.7 minutes (95% CI 9.1-12.4), CE with targeted biopsies was still found to be less costly and more effective than SDWL with random biopsies [5,22]. Furthermore, in comparison to SDWL colonoscopy, this cost-effectiveness analysis still found that CE with random and targeted biopsies would offset this incremental increase in cost [22]. Since the publication of these studies, the role of SDWL endoscopy has been replaced by the adoption of HDWL endoscopy to which ongoing research transitioned to comparative studies regarding the use of HDWL versus CE.

High-definition *vs* chromoendoscopy

The SCENIC consensus offers a conditional recommendation with low quality of evidence to suggest the use of chromoendoscopy over high-definition endoscopy (84% agreement) [5]. The basis for and strength of this recommendation is based on limit data which came from a single study which was actually designed to address concerns about the generalizability of CE to community practice due increased procedural length and lack of proven interobserver agreement [23]. They completed a prospective trial in which 6 endoscopists without prior experience in the use of CE performed HDWL endoscopy followed by CE in 75 patients with photo documentation of both normal and dysplastic lesions to allow for interobserver comparison [23]. Overall, there was a significant increase in dysplasia detection for CE plus HDWL versus HDWL alone (9.3% *vs* 21.3%, p=0.007) with high ratings for interobserver agreement with kappa scores of 0.91 for HDWL and 0.86 for CE [23]. Withdrawal times were longer for those performing fewer than 5 procedures, however stabilized above 5 procedures and was similar for those with 5 to 14 versus greater than 15 procedures suggesting a relatively minimal learning curve for the technical aspects of CE [23].

Since the publication of the SCENIC consensus, a multicenter, prospective randomized control trial across 9 tertiary teaching hospitals in South Korea evaluated 210 patients with long-standing ulcerative colitis currently in clinical remission compared HDWL-R (high-definition white light with random biopsies) to HDCE-T (high-definition chromoendoscopy with targeted biopsy) [24]. Overall, HDCE-T was not superior to HDWL-R for detection of colitis associated dysplasia (3.9% *vs* 5.6%, p=0.749), although HDCE-T did demonstrate a trend for improved detection of any colorectal neoplasia (20.6% *vs* 12.0%, p=0.93) [24]. Secondary analysis also highlighted important findings including similar withdrawal time between the two groups (17.6 *vs* 16.5, p=0.21) and significant decrease in the number of biopsy samples with HDCE-T *versus* HDWL-R (9 *vs* 34, p<0.001). The observation about similar withdrawal times is an important findings, as the authors noted that prior meta-analyses had demonstrated an increase in procedure time by up to 11 minutes [5,25]; however, these studies had heterogeneity in the type of chromoendoscopy utilized with respect to spray catheter or automated water lavage pump. A similar finding of non-inferiority for HDWL was demonstrated ,in which HDWL was sufficient for the detection of dysplasia, adenocarcinoma, or all neoplastic lesions [26]. Notably, this study also utilized video chromoendoscopy (VCE), which was found to also be non-inferior to chromoendoscopy. The application of the VCE however, cannot be generalized because it is a proprietary software included only in Pentax endoscopes [26].

In summary, there is equivocal evidence to definitely support the use of CE over HDWL for routine dysplasia surveillance in long standing IBD. There may be some difference in regards to the need for targeted versus random biopsies and also the role of CE following the detection of dysplasia; however, these will be discussed separately in subsequent sections of the chapter. Regardless, the use of CE is still strongly embraced among specialty IBD providers given its clear benefit when thoroughly inspecting a lesion of interest. Figure 1 demonstrates the contrast between CE and HDWL endoscopy where a sigmoid lesion confirmed as adenomatous demonstrates subtle mucosal changes extending out from the base of the larger polypoid portion of the lesion; whereas the border of sessile portion is difficult to distinguish from surrounding mucosa on HDWL, the

uptake of contrast dye in CE accentuates the pit pattern and more clearly demarcates the peripheral border of the lesion as illustrated with the yellow arrows. Using the Kudo pit pattern classification, this lesion would be characterized as a Type IIIL (long tubular pits) which is consistent with a neoplastic tubular adenoma [27].

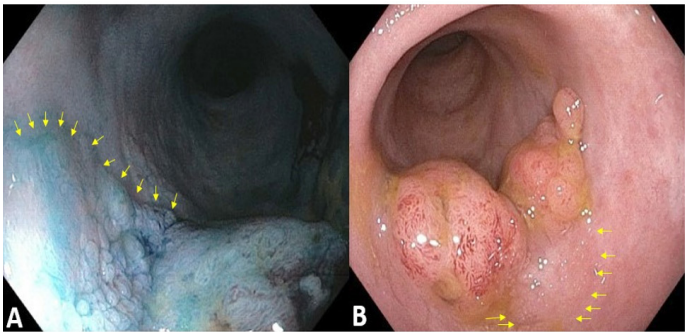

Figure 1: Chromoendoscopy (CE) versus High-Definition White Light (HDWL) on Sigmoid Lesion.

A: CE demonstrating subtle mucosal changes extending out from the base of the large polypoid lesion outlined by the yellow arrows.

B: HDWL image with arrows showing the corresponding area from the CE image, which appears virtually indistinguishable from the surrounding normal mucosa.

Narrow band imaging

When performing surveillance colonoscopy, the SCENIC consensus does not recommend the use of NBI in place of standard-definition white light (84% agreement; conditional recommendation; low-quality of evidence), high-definition white light (80% agreement; conditional recommendation; moderate quality of evidence), or chromoendoscopy (90% agreement; conditional recommendation; moderate quality of evidence) [5].

Compared to WL endoscopy, three studies were identified which found no significant difference between NBI and WL; however, fewer dysplastic lesions were identified with NBI than WL in all studies [28-30]. This lack of clear benefit was the basis for the reason behind no recommendation for the use of NBI.

The evidence for NBI in comparison to CE was also mixed with the SCENIC consensus reviewing four studies and completing a meta-analysis; all of these failed to show a significant difference (meta-analysis absolute risk 6%, 95% CI -1 to 14%) [5]. Since the publication of SCENIC, a prospective multicenter trial including 131 patients randomized CE or VCE with NBI and performed targeted biopsies of visible lesions and the surrounding tissues [31]. Overall, there was no significant difference between the two with a neoplasia detection rate of 21.2% for CE and 21.5% for NBI (OR 1.02, 95% CI 0.44-2.35) [31]. Notably, procedural times were an average of 7 minutes shorter in the NBI group [31].

In summary, despite new recommendations for proficiency in and adoption of NBI to aid in optical diagnosis and classification of lesion histology in the 2020 US Multi-Society Task Force on Colorectal Cancer recommendations for endoscopic removal of colorectal lesions, the role of NBI in IBD surveillance remains equivocal [32]. Given the small size and heterogeneity of the prior studies, no strong recommendation can be made for or against NBI. While it is unclear the future role of NBI, it would not be unreasonable to suspect that it may emerge as a potential alternative to CE, especially when the increased adoption of the technique in other endoscopic procedures improves general proficiency in the technique along with continued refinements to the image enhancement by endoscopy manufacturers.

Summary

Current endoscopic technology has seen remarkable advancements in particular with the advent of HDWL, refinement of CE technique, and new computer aided imaging with NBI. Figure 2 offers a comparative view of these different technologies on the same cecal sessile serrated adenoma, which were all used to aid in polyp characterization prior to successful endoscopic mucosal resection. Kudo pit pattern with CE shows a Type II pattern (large star-shaped pits) which are often seen in sessile serrated polyps, and NICE classification is best characterized as NICE I (similar color to the background mucosal without increased vessels) at the periphery with the central portions demonstrating NICE II (browner color relative to background with more tubular vessels) [19,27].

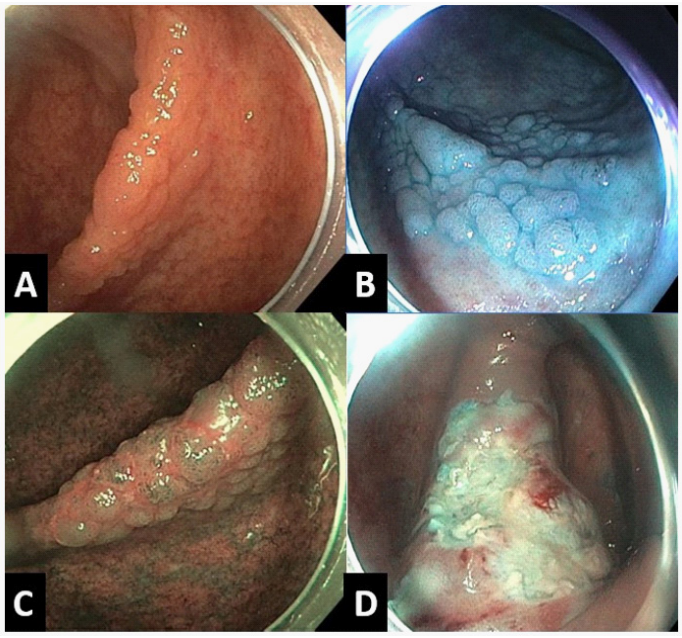

Figure 2: Comparative Views of a Dysplastic Lesion with Varying Imaging Techniques.

A: High-definition white light;

B: Chromoendoscopy;

C: Narrow Band Imaging;

D: Post endoscopic mucosal resection.

The existing literature is somewhat obtuse given the heterogeneity across included technologies, although in general, expert recommendations remain consistent. Namely that HDWL examinations have greater detection of dysplasia than SDWL and also that while more recent studies are equivocal for recommending CE over HDWL for surveillance examinations, those with low grade dysplasia on biopsies should clearly undergo a CE examination in expert hands. NBI also offers an adjunctive tool, but currently this would seem to apply more towards detected lesions and not for complete surveillance colonoscopies. More detailed review of literature for the application of these technologies and management of dysplasia is discussed in the next section.

Endoscopic management of dysplasia

The management of dysplasia in IBD can largely be considered in one of the four domains: how to best detect dysplasia; what to do when finding dysplasia; how to endoscopically manage dysplasia; and, how to best endoscopically survey dysplasia. This section will seek to explore each of these questions by reviewing the existing literature and also expert opinions to provide clinical recommendations for best practice techniques.

Targeted *vs* random biopsies

Historically, recommendations for dysplasia surveillance in patients with extensive IBD have advocated for the use of random biopsies, including a minimum of 33 biopsies taken in a 4-quadrant fashion every 10 cm throughout the colon in addition to any concerning areas warranting focused target biopsy [17]. For those at high risk, recommendations were even to take 4-quadrant biopsies every 5cm in the lower sigmoid and rectum among UC patients [17,33].

The premise for this recommendation was that dysplastic changes (formerly colitis-associated neoplasia) were thought to be undetectable with significantly older fiber optic endoscopes, which are no longer in clinical use. Retrospective studies however, have demonstrated that even with current standard definition endoscopes most dysplasia is visible if appropriately recognized [2,34,35]. In fact, the SCENIC consensus noted that review of prior studies comparing targeted versus random biopsies revealed that dysplasia was detected by random biopsy in approximately 10% of patients and on targeted biopsy in the other 90% [5]. Many experts have been split on the recommendation for random versus targeted biopsies, with a greater proportion agreeing for targeted biopsies with chromoendoscopy [18,36]. Even so, consensus was not achieved in the SCENIC consensus with 45% agreement and 30% disagreement for random biopsies with HDWL and 25% agreement and 60% disagreement for CE [5].

The controversy over the optimal biopsy methodology is due largely, to lack of strong supporting evidence-based medicine. Since the publication of SCENIC there has been some additional insight, including a retrospective review of 484 patients who underwent dysplasia surveillance by any means [37]. Overall, neoplastic lesions were detected in 8.2% of random versus 19.1% of targeted biopsies (95% CI 13.4-26.5, p<0.001) [37]. Comparison of patients by HDWL, VCE, or CE did not demonstrate any significant differences. Of note, review of the random biopsy procedures demonstrated a median of 23 biopsies with a range from 4 to 50, suggesting that the recommendations for at least 33 biopsies is not always being followed in clinical practice and may partially explain why random biopsies did not perform as well [37].

Further support for the role of targeted biopsies comes from a multicenter randomized trial in Japan using HDWL. This trial compared random and targeted biopsies demonstrating a similar portion of neoplasia (11.4% *vs* 9.3%, p=0.617), but targeted biopsies resulted in a significantly shorter procedure length (41.7 *vs* 26.6 minutes, p<0.001) [38]. Another important observation in this study was that no neoplastic tissue was found in areas without prior inflammatory activity [38].

Overall, the evidence regarding the use of targeted versus random biopsies remains imperfect, however with the advent of HDWL endoscopy current literature suggests improved rates of neoplasia for targeted over random biopsies. This practice pattern also appears to be more adaptable to real world practice with shorter procedure times and likely reduced pathology costs from fewer samples. As such, it would seem most appropriate to advocate for the use of targeted biopsies with HDWL or CE, in particular with close attention to prior areas of inflammation for which random biopsies could be obtained of those sections.

Finding of "invisible" dysplasia

According to the SCENIC consensus, the finding of "invisible" dysplasia, which is defined as dysplasia identified on random (non-targeted) biopsies of colon mucosa without a visible lesion, on white light surveillance colonoscopy should prompt consideration of referral to an expert in chromoendoscopy, with 100% agreement but very-low-quality evidence [5]. The consensus notes no studies on outcomes of endoscopic surveillance versus colectomy and only 4 studies on CRC incidence after diagnosis of invisible dysplasia, which occurred in 6% over a follow up period ranging from 15 to 50 months [39-42]. The pressing reason for referral for CE therefore appears to be driven by the belief that these patients may have multifocal invisible low-grade dysplasia which confers a greater risk for CRC which may be better detected with CE [5].

Outcomes following this recommendation remain unclear. Rubin et al published results from a retrospective review of patients referred to their tertiary center to undergo CE for dysplastic lesions, noting 62 referrals with reidentification of the lesion in only 42% (26/62) cases [43]. Furthermore, 12 additional synchronous lesions were identified including 9 low-grade dysplasia, 1 high-grade dysplasia, and 2 cancers [43]. Despite being a small retrospective study, there are a number of important observations noted from this study. First, this closely assimilates "real world practice" and demonstrates that overall, there is likely insufficient documentation detailing the location and morphology of lesions in addition to underutilization of endoscopic tattooing of concerning lesions. Second, the finding of additional lesions in 15% of patients supports referral to experts for completion of CE, especially to find synchronous lesions.

Based on updated literature, the most recent American College of Gastroenterology (ACG) guidelines noted that once dysplasia is detected then the patient should be considered for CE for enhanced visualization and removal of lesions of suspect concern for neoplastic change [2,43,44]. Additionally, they note that if no dysplasia is found on CE then the risk for advanced dysplasia on follow up is very low and those with consecutive negative examination could be considered for longer surveillance intervals [2,45-47].

Endoscopic management and surveillance of dysplasia

Clearly, patients with lesions that are not deemed amenable to endoscopic resection or who have multifocal dysplasia, should be referred to colorectal surgery for further evaluation and management with proctocolectomy [2]. As defined by the SCENIC consensus, an endoscopically resectable lesion has the following characteristics: (1) distinct margins of the lesion could be identified, (2) the lesion appears to be completely removed on visual inspection after endoscopic resection, (3) histologic examination of the resected specimen is consistent with complete removal, and (4) biopsy specimens taken from mucosa immediately adjacent to the resection site are free of dysplasia on histologic examination [5]. For those with endoscopically resectable lesions, referral to a therapeutic endoscopist with

experience in advanced polypectomy should be heavily considered owning to the challenging nature of these polypectomies. Highlighting this, a recent multicenter study of patients undergoing endoscopic submucosal dissection for dysplasia in IBD found that 73% (33/45) of lesions had evidence of submucosal fibrosis [48].

Once the dysplastic lesion has been endoscopically removed, the SCENIC consensus recommends resumption of surveillance colonoscopy rather than colectomy. Suggested intervals for this surveillance colonoscopy are 3-6 months for larger (>15mm) sessile lesions removed piecemeal *via* endoscopic mucosal resection or endoscopic submucosal dissection and 1 year for small polypoid lesions (<15mm) removed en-bloc [5]. If the initial repeat endoscopic examination is negative then repeat colonoscopies at 1 year intervals is recommended.

Evidence supporting these recommendations is somewhat limited, owing to the wide data-range of studies across different periods of endoscopic technology. Still a systematic review of 10 studies including 376 patients over a mean of 54 months found an annualized incidence of 0.5% for colorectal cancer [49]. Siegel et al looked at patient preferences to undergo colectomy for reduction of cancer risk in IBD and found that among 199 UC patients, the average risk of colon cancer to undergo surgery "right now" would be 73%, suggesting that patient are more willing to undergo surveillance colonoscopies over the long term than surgical intervention [50].

Most recently, a systematic review and meta-analysis including 18 studies, 1037 IBD patients, and 1428 colonic lesions undergoing endoscopic resection and surveillance found supporting evidence that the risk of CRC remains low.[51] Overall, the pooled risk per 1000 patient years was 2 for CRC (95% CI, 0-3), 2 for high grade dysplasia (95% CI, 1-3), and 43 for recurrence of any lesion (95% CI, 30-57). For recurrent lesions, 55% were able to be managed with endoscopic mucosal resection. In total, 9.9% (05% CI, 6.5-14.7) of patients required surgical resection during the follow up period with over half due to confirmed diagnosis of adenocarcinoma (30.7%) and unresectable and/or metachronous lesion (23.9%).[51] While clearly there are limitations to this data due to heterogeneity of the studies and patient populations, overall the results support the role of endoscopic resection and surveillance of dysplastic lesions in IBD. With this approach, overall incident rate of CRC is low, with approximately 90% of patients avoiding invasive surgical intervention.

Summary

Despite prior recommendations advocating for random biopsies (4) every 10 cm or less throughout the colon, more recent evidence has suggested that targeted biopsies provide comparable results when performed with high HDWL or CE. This approach is associated with decreased pathologic tissue acquisition and procedural time. The distinction between HDWL and CE with targeted biopsies is still a point of ongoing investigation with varying reported outcomes, potentially related to study design and heterogeneity. For the finding of "invisible" dysplasia, both evidence-based literature and expert opinion would favor endoscopic assessment with CE, which has improved dysplasia detection over WL endoscopy. For endoscopically resectable lesions, strong consideration should be given for referral to a therapeutic endoscopist experienced in advanced polypectomy given the challenging nature of these cases. Once lesions have been endoscopically removed, an intensive surveillance routing with repeat colonoscopy in 3-6 months is reasonable prior to lengthening follow up time. For patients with repeatedly normal surveillance examinations, there is still limited evidence for how to best lengthen out surveillance intervals, however this is likely to be a focal point for further research as we expand our knowledge about disease severity and its impact on individual patient risk for CRC.

Emerging technologies: AI in IBD surveillance

Artificial intelligence (AI) is a discipline in computer science aimed at the assimilation human intelligence by computers, which has emerged as a leading field in research and development in medicine and gastroenterology. Application of AI utilizes two main forms: Machine Learning (ML) and Deep Learning (DL) [52,53]. Machine learning is a form of AI which involves a set of algorithms that learns from training data to perform a given task, whereas in deep learning the machine analyzes and processes the data and creates its own neural network [53,54]. The neural networks of DL, such as deep neural network (DLL) and Convolutional Neural Network (CNN), closely resembles neural network of animal biology in which each neuron or node is interconnected with each other and works systematically to perform a specific task [53,54]. Utilizing DL and its neural network, researchers have developed Computer Aided Diagnosis Systems (CADS) to assist in detection and classifications of lesions during endoscopy [53,54]. There are two major CADS actively researched to enhance polyp detection, adenoma detection rate, and optical biopsy: automated polyp detection (CADe) and automated polyp characterization (CADx) [55]. More specifically, CADe applies to computer-aided polyp detection utilizing white-light endoscopy for image analysis for the purpose of detecting polyps with the overall goal to prevent missing polyps during colonoscope withdrawal [55]. In contrast, CADx is termed for computer-aided polyp characterization and utilizes different techniques such as magnifying narrow band imaging (mNBI), white-light endoscopy, magnifying chromoendoscopy, endocytoscopy, confocal laser endomicroscopy, spectroscopy, and autofluorescence endoscopy to provide real-time characterization and prediction of polyp pathology [55].

Given that AI is still an emerging field of research, current research is largely focused on optimizing the technology for polyp detection and characterization in general endoscopy and colorectal cancer screening. There have been some recent publications specific to AI in IBD, although they are still in the early stages of development and pertain largely towards diagnosis, risk prediction, disease activity, and clinic outcomes with limited focus on dysplasia detection in IBD [56,57]. As a result, the remainder of this section will focus on the current evidence for CADe and CADx systems in polyp detection and characterization whose results will likely offer future translation and integration into the IBD dysplasia management paradigm.

Several studies have recently been published concerning the use of CADe for polyp detection. Polyp detection CADe systems were developed as early as 2016 and one of these early systems analyzed still images of 31 different polyps from endoscopic videos demonstrating a sensitivity of 70.4% and specificity of 72.4% for polyp detection [58]. More recent CADe systems have improved the sensitivity and sensitivity of their models significantly. For example, Wang et al. developed a DL alogritm using data from 27,113 colonoscopic images across 1,133 patients with an overall sensitivity of 94.4%, specificity of 95.9%, and Area Under the Receiver Operating Characteristic Curve (AUROC) of 0.984 in polyp detection [59]. Further promising data

regarding the accuracy of these systems comes from a study which prospectively compared a CADe system against trained endoscopists with high adenoma detection rate (>35%) [60]. Among the 606 polyps included, endoscopists and CADe diagnostic accuracy was 98.2% and 96.5%, respectively, confirming a non-inferiority of the CADe system ($p<0.001$) [60].

Similar to CADe systems for polyp detection, CADx systems have offered encouraged results for the characterization of colon polyps. Chen et al developed a CADx with DNN to detect and analyze diminutive colorectal polyps utilizing 1,476 narrow-band images of neoplastic polyps and 681 images of hyperplastic polyps to train the CADx system; this system was then tested on 96 neoplastic and 188 hyperplastic polyps with a sensitivity and specificity of 96.3% and 78.1%, respectively [61]. Similar results were found by Shanchez-Montes validating a CADx system for white light (WL) endoscopy on 225 different polyps and demonstrated accuracies of 92.3% and 89.2% in discerning dysplastic and non-dysplastic polyps, respectively [62].

While these systems are for the most part, still investigational and not entirely ready for prime-time, they do offer encouraging results for future wide-spread adoption in clinical practice as an adjunct for polyp detection and characterization. In particular for IBD when lesions may often be subtle, these systems may offer a robust integrated solution for enhancing detection of dysplastic lesion over the current existing endoscopic technologies. GI Genius (Cosmo Pharmaceuticals N.V., Dublin, Ireland) is the first FDA approved AI device for polyp detection, which is a CADe system enabling real-time video processing for polyp detection during colonoscopy [63,64]. The initial validation study of GI Genius demonstrated a remarkable sensitivity (99.7%) in detecting a polyp and a faster reaction time of detection compared to endoscopists [64]. Subsequently, Repici et al. performed a multicenter randomized trial utilizing GI Genius to analyze the Adenoma Detection Rate (ADR) among 700 patients undergoing high-definition colonoscopy with or without CADe, demonstrating an ADR of 54.8% with CADe and 40.4% without [65]. Additionally, CADe group was found to have a higher rate of adenoma per colonoscopy (APC) compared to that of control [65].

While not yet available for use in the United States, EndoBRAIN (Olympus Corporation, Tokyo, Japan) is a CAD system for endocytoscopy with 2 modes including stained mode for analyzation of cell nuclei and crypt structure and NBI mode for assessment of microvessels [66-69]. Kudo et al. performed a multicenter retrospective study and compared the diagnostic accuracy of EndoBRAIN against 30 endoscopists [69]. EndoBRAIN was initially trained using 69,142 endoscytoscopic images and then tested on endocytoscopic images of 100 polyps; in this comparison, EndoBRAIN identified colonic lesions with sensitivity, specificity, and accuracy of 96.9%, 100%, and 98%, respectively [69]. It also discerned neoplastic lesions from non-neoplastic lesions with sensitivity of 96.9%, specificity of 94.3%, and accuracy of 96.0% [69]. Finally, the time to diagnosing a lesion was significantly faster with EndoBRAIN compared to that of endoscopists [69]. Given the remarkable results and diagnostic accuracy, EndoBRAIN was approved for clinical use by the Japanese regulatory agency.

Artificial intelligence and its application in endoscopy have shown significant utility in detecting and characterizing polyps. Although the technology lacks specific studies and data on IBD surveillance, AI and its neural networks are rapidly evolving. The recent approval of these devices will further contribute to reducing colorectal malignancies in general and IBD populations, and the collected data and experience will provide additional guidance to integrating AI in surveillance colonoscopies in IBD.

Conclusion

Colonoscopic surveillance remains a foundation in the long-term care of patients with UC and colonic CD. Advances in technology have allowed for the early identification and endoscopic removal of dysplastic lesions, significantly reducing the need for surgical intervention. Such tools have including high-definition endoscopy and chromoendoscopy, but also advances in techniques for endoscopic mucosal resection and endoscopic submucosal dissection. The emerging applications of AI promise to bring new technology to endoscopy offering real-time guidance to assist in polyp detection and histologic characterization. While these AI systems may not be ready for widespread application at present, there is no question AI is poised to revolutionize IBD surveillance and will be a welcome addition into the endoscopic armament, particular in these high-risk populations.

Chapter highlights

- Patients with long-standing (>8 years) ulcerative colitis or Crohn's disease with greater than one-third colonic involvement should undergo surveillance for CRC.
- The overall incidence of CRC in IBD patients is best estimated at 5% after 20 years of disease activity.
- Surveillance examinations should be performed during periods of controlled and quiescent inflammation, with a particular emphasis on high quality bowel preparation.
- High-definition endoscopes should be utilized if performed white-light endoscopy.
- There is limited evidence to clearly support the routine use of chromoendoscopy over high-definition white light endoscopy.
- Narrow-band imaging is not a recommended alternative to chromoendoscopy.
- For high-definition white light or chromoendoscopy, targeted biopsies are associated with shorter procedure times without any significant decrease in dysplasia detection.
- If invisible dysplasia has been detected on white light endoscopy, patients should be referred to undergo chromoendoscopy by an expert in the technique.
- Dysplastic lesions should be referred to therapeutic endoscopists for evaluation of endoscopic resection.
- For large (>15mm) sessile lesions removed in piecemeal, it is reasonable to perform initial surveillance colonoscopy at 3-6 months. If this initial examination is normal, then patients should undergo colonoscopies at 1-year intervals.
- Artificial Intelligence advancements in endoscopy have led to the creation of computer aided diagnosis systems (CADS) for which the current focus is on polyp detection (CADe systems) and polyp characterization (CADx systems). While these systems are not yet ready for prime-time, preliminary outcomes offer encouraging results to suggest these AI systems may offer a seamless, real-time integration into clinical practice to enhance polyp detection and characterization.

Conflicts of interest

David A Johnson, MD-clinical investigator DocBot.

None relevant for all other authors.

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