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**Screening and surveillance methods for dysplasia in IBD patients. Where do we stand?**

Galanopoulos M *et al.* Screening and surveillance methods for dysplasia in IBD patients. Where do we stand?

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**ABSTRACT**

Patients with long-standing ulcerative colitis (UC) and extensive Crohn’s colitis (CC) are at increased risk for dysplasia and colorectal cancer (CRC). Several studies have shown that UC extending proximal to the rectum, CC involving at least 1/3 of the colon, co-existence of primary sclerosing cholangitis (PSC), undetermined or unclassified colitis, family history of CRC and young age at diagnosis appear to be independent risk factors for inflammatory bowel disease (IBD)- related CRC. Therefore, screening and surveillance for CRC in IBD patients is highly recommended by international and national guidelines, whilst colonoscopy remains the unequivocal tool in order to detect potentially resectable dysplastic lesions or CRC at an early stage. Although the importance of screening and surveillance is widely proven, there is a controversy regarding the time of the first colonoscopy and the criteria of who should undergo surveillance. In addition, there are different recommendations among scientific societies concerning which endoscopic method is more efficient to detect dysplasia early, as well as the terminology for reporting visible lesions and the management of those lesions. This article concisely presents the main endoscopic methods and techniques performed for detecting dysplasia and CRC surveillance in patients with IBD focusing on their evidence-based accuracy and efficiency, as well as their cost-effectiveness. Finally, newer methods are mentioned, highlighting their applicability in daily endoscopic practice.

**Key words:** Ulcerative colitis; Crohn’s disease; Inflammatory bowel disease; dysplasia; Colorectal cancer; Endoscopy; Chromoendoscopy; Surveillance; Virtual Chromoendoscopy systems; Confocal laser endomicroscopy

**Core tip:** There is an established association between inflammatory bowel disease (IBD) and colorectal cancer (CRC). Therefore, surveillance of these patients for CRC is crucial and recommended by international guidelines. In this review we present the main endoscopic methods and techniques performed for detecting dysplasia and CRC surveillance in patients with IBD, highlighting chromoendoscopy with targeted biopsies as the gold standard method. Finally, newer methods are mentioned, examining their applicability in daily endoscopic practice.

**Audio Core Tip**

Galanopoulos M, Tsoukali E, Gkeros F, Vraka M, Karampekos G, Mantzaris GJ. Screening and surveillance methods for dysplasia in IBD patients. Where do we stand?

**INTRODUCTION**

Patients with IBD have a higher incidence of CRC compared to the general population, even though only 1% of all CRC cases are attributed to IBD[1]. The incidence rates reported by *Eaden et al.*, as well as from the St. Mark’s group in the United Kingdom, showed comparable cumulative probabilities of CRC and dysplasia, approximately 8% and 18% by 20 and 30 years of ongoing disease, respectively [2,3]. According to *Bernstein et al*, both Crohn’s disease (CD) and UC patients face an increased risk for colon cancer (relative risk (RR) 2,64 and 2,75, respectively)[4]. Factors linked to an increased incidence of CRC include: prolonged duration of colitis, extensive colonic involvement, presence of PSC, positive family history for CRC and, according to some studies, younger age of onset and severity of inflammation[1,5–9] (Table 1). Oncogenesis in IBD has been well described as result of chronic inflammation, leading via low- and high- grade dysplasia, finally, to CRC[1,10,19–24,11–18] (Figure 1). Dysplasia is divide into two categories: 1) Endoscopically visible dysplastic lesion e.g polyps, which are detected by targeted biopsies or resection of endoluminal masses 2) Endoscopically invisible dysplasia which is detected by blinded random biopsies on endoscopically normal lumen and is characterized as the most dependable marker for increased CRC risk in IBD patients[1,25,26]. The resection of visible dysplasia, in combination with a rigorous follow-up program has been shown to be a safe alternative to colectomy for select patients [27,28]. On the other hand, a study by *Picco et al* showed that the detection rate for dysplasia with the use of white light endoscopy (WLE) was 9,3%, compared to 21,3% when using both WLE and dye-spray chromoendoscopy (DCE)[29]. This demonstrates the need for the implementation of a surveillance strategy in IBD patients based on better techniques and technologies, aiming at reducing the prevalence of metachronous lesions during follow-up. However, uncertainties exist regarding the soundness of this approach on preventing CRC. In a recent systematic review, people undergoing periodic surveillance for CRC were not found to have lower mortality when compared to those under no surveillance (RR 0.81, 95%CI 0.17 to 3.83)[30,31].

Nevertheless, the current recommendations favor DCE with targeted biopsies of any identified lesions[1,26,32,33] (Figure 2). Whenever DCE is not available, WLE with random, four quadrant biopsies every 10 cm should be performed with additional targeted biopsies from visible lesions. Other endoscopic modalities, like narrow band imaging, i-SCAN and autofluorescence imaging, did not achieve superior dysplasia detection rates when compared to standard (SD)- or high-definition (HD) WLE in randomized controlled trials[34–39].

Taking all these into consideration, the aim of our review is the brief and up-to-date description of the basic screening endoscopic modalities, as well as their efficacy and accuracy for CRC surveillance in IBD patients.

**Standard-definition and high-definition white light endoscopy**

The standard method in CRC surveillance has until recently been SD colonoscopy, with the use of targeted as well as random quadrant biopsies every 10 cm, which amounts to, at least 33 biopsies to achieve 90% confidence of detecting dysplasia. However, this technique ultimately inspects less than 1% of the mucosal surface of the colon[40]. According to a Dutch study examining long-standing UC, the overall rate of dysplasia detection with SD colonoscopy was 0,19[36]. With the advent of HD endoscopes and monitors, the endoscopist is able to better identify dysplastic lesions. A study by *Subramanian et al* comparing SD to HD colonoscopy for dysplasia screening in UC, reported a three-fold increase in the yield of the HD endoscope combined with targeted, as well as random biopsies, especially in the right colon. Based on the aforementioned study, the SCENIC consensus statement by American Society for Gastrointestinal Endoscopy (ASGE) favors HD- over SD-WLE when implementing a surveillance program, even though the HD cost remains a limitation[33]. This improvement in detection of dysplastic lesions by HD-WLE and targeted-biopsy sampling changed the therapeutic considerations regarding colectomy, favoring more conservative approaches[41]. Furthermore, it was pointed out that the increased turnout with HD colonoscopy is probably a true reflection of the increased yield of this technique[41]. Nevertheless, based on the same study, neither significant change in the detection of lesions with high grade dysplasia, nor early carcinoma or flat lesions was observed.

On the contrary, the study by *Van den Broeck et al* showed no substantial difference in clinical outcomes for patients, in whom low grade dysplasia was revealed using random biopsies, thus advocating the use of improved visualization through advanced techniques[36,41].

Concluding, even though the most widespread technique for dysplasia surveillance in IBD until recently has been the WLE with random biopsies, it is arduous and protracted[40]. Furthermore, the diagnostic reliability of WLE is challenged in a recent review, which found a sensitivity of 76%[42]. Therefore, this methods practicability has been clearly questioned and the research for the development of diagnostic modalities is supported[43].

**Random biopsies**

Four quadrant biopsies every 10 cm throughout the colon has been the gold standard of IBD surveillance for more than 30 years. This approach originates from the theory of "flat dysplasia", which suggests that dysplasia is difficult to visualize in colitis-affected mucosa[40,44]. Random biopsy only samples less than 1% of the luminal mucosa; has a subpar detection rate (<2 per 1,000 biopsies taken) and when used in conjunction with advanced endoscopic techniques, it does not affect clinical decisions. [44]. A large retrospective analysis by *Van de Broeck et al* reviewing 1010 colonoscopies during 10 years of surveillance stated that the result of random biopsy surveiilance  was poor, and neoplasia was detected only in four patients with random biopsies. Additionally, neoplasia was macroscopically visible in 94% of colonoscopies[43,44]. Current guidelines by British Society of Gastroenterology (BSG) and ASGE advocate the use of DCE without the need for random biopsies, however it is suggested that random biopsies be acquired during HD colonoscopy, if DCE is not available or technically feasible[26] . Moreover, the latter remains a reasonable alternative if the presence of inflammation, pseudo-polyposis, poor preparation, or an area of poorly visualized mucosa significantly lowers the yield of DCE[26,45].

**Dye-spray chromoendoscopy**

Several studies have proven the efficacy of DCEin the detection of dysplasia in patients with IBD. DCE may reduce the need for random biopsies and may allow prolonged surveillance-interval, leading to costs reduction, as well as increasing the detection sensitivity of dysplastic lesions per examination[46].

This technique helps to augment dysplasia detection by topical application of dye on the colonic mucosa during colonoscopy. Areas that are macroscopically elevated or depressed, friable, obscure in vasculature, and with a villous or nodular pattern, can be detected more easily and biopsies can be taken. The most common dyes that are used are methylene blue and indigo carmine[47]. Dye solution can be sprayed by catheter, or flushing pumps, or as controlled release tablets taken with bowel preparation[48]. When performing DCE, it is important to avoid active disease and to have adequate bowel preparation. Paris classification seems to be the standard method to describe any visible lesion, and targeted biopsies should be taken from any suspected area. If the lesion is well-defined, en-bloc endoscopic resection should be performed and biopsies should be taken from the adjacent mucosa. In case the lesion is unresectable, the endoscopist should take biopsies and tattoo the area.

*Kiesslich et al* were the pioneers conducting a large randomized study with 263 individuals with long-standing UC[49]. In the DCE-group, there was a statistically important correlation between the endoscopic estimation of the level and extent of inflammation of the colon (p = 0.0002) and the histology report, when compared to WLE (p = 0.0002) (89% vs. 52%; p< 0.0001). Additionally, more targeted biopsies were possible and these biopsies detected significantly more intraepithelial neoplasia when performing DCE (32 vs. 10; p= 0.003). In a well-designed prospective study, *Hurlstone et colleagues* examined 350 patients with long-standing UC undergoing colonoscopy surveillance with high-magnification chromoscopic colonoscopy (HMCC) comparing the data with matched controls who had undergone WLE[50]. The HMCC-group found significantly more intraepithileal neoplasias (INs) compared to controls (69 vs. 24; p<0.0001), and only 0,16% of the non-targeted biopsies have shown INs versus 8% from the targeted biopsies. Furthermore, *Marion et al.* studied 102 patients with IBD who underwent in a single examination, initially a WLE with random biopsies, then a targeted biopsy protocol and finally, DCE with targeted biopsies[51]. They reported that biopsies obtained by the latter method detected significantly more dysplastic lesions than random biopsies with WLE (p = 0.001), as well as more than WLE with targeted biopsies (p= 0.057).

According to *Subramanian et al.* meta-analysis study including a large number of patients, the overall difference between the DCE and WLE in the detection of dysplasia was approximately 7% (95% Cl 3.2-11.3), with the former showing a better rate of dysplastic lesions detected by targeted biopsies, as well as a higher rate of detection for flat lesions at 27% (95% C: 11.2-41.9)[52]. On the other hand, the omission of random biopsies during chromoendoscopy will result in missing endoscopically invisible dysplasia. According to another meta-analysis, *Wu et al.* reported that DCE offers median to good sensitivity and a very good accuracy for revealing lesions with dysplasia+ in UC after analyzing six randomized controlled trials with 1.528 patients[47]. The pooled sensitivity and specificity for DCE with targeted biopsies were 83.3% (95% CI: 35.9–99.6%) and 91.3% (95% CI: 43.8–100%) respectively, with conventional colonoscopy demonstrating lower rates. *Soetikno et al.* in a well-designed meta-analysis with 665 patients with IBD, demonstrated that the pooled positive percentage of DCE over WLE for the discernment of dysplasia of any grade per patient was 7% (95% CI: 3.3%-10.3%), as well as the possibility to miss dysplasia was 93% lower by performing chromoendoscopy with targeted biopsies (the pooled OR was 0.07;95% CI 0.03-0.21)[53]. Interestingly, according to a prospective study, *Marion et colleagues* showed that apart from the superiority of DCE when compared to WLE, a DCE examination without any findings was considered as the most probable indicator for a patient without any level of dysplasia, whereas an exam with any sort of findings was positively correlated with earlier referral for colectomy(hazard ratio, 12.1; 95% CI, 3.2-46.2)[54].

Nevertheless, lately, the advantages of DCE over WLE have come into question, as well as the practicability of applying DCE in a real world setting of hectic endoscopy units. Trying to highlight this problem, a large retrospective non-randomized trial with different types of endoscopes used over time showed that the performance of DCE for IBD surveillance did not increase detection of dysplasia compared with WLE with targeted and random biopsies (11 % vs 10 %, p = 0.80)[55]. The number of lesions with neoplasia was also comparable between the DCE and WLE groups (p=0.30).

As a final point, an interesting cohort analysis regarding cost-effectiveness was conducted by *Konijeti et al,* that compared DCE with targeted biopsies to WLE with random biopsies at various surveillance intervals and no surveillance at all[56]. Chromoendoscopy was more efficient in the detection of dysplasia and cost effective when compared with WLE. DCE exhibited cost-effectiveness relative to patients not undergoing any surveillance when performed at0020intervals bigger than 7 years.

**Virtual Chromoendoscopy systems (VCE)**

Technological progression has enabled newer modalities based on older technologies for mucosal assessment. Given the success rate of chromoendoscopy to assess colonic mucosa, the newest endoscopic devices have filters and algorithms that enable the mimicry of chromoendoscopy by filtering some light wavelengths to better underline abnormal tissues, while foregoing the limitating factors of chromoendoscopy. Dye-less or virtual chromoendoscopy has been developed by three major manufacturers for their respective endoscopic platforms. Narrow Band Imaging (NBI) filters out red and green light bands while contributing more to blue light bands at the 415nm wavelength. This modality allows for visualization of the vasculature of the upper mucosa and different patterns correlating to different degrees of mucosal inflammation and predicts disease relapse. In the same vein, the i-Scan system provides detailed analysis, which is based on principles similar to NBI, with resolutions higer than HD television parameters that allow for the processing of light through specific algorithms. This process provides detailed analysis based on vessel, mucosal pattern or surface architecture (i-Scan v, i-Scan p and i-Scan SE, respectively), with each analysis being readily available during endoscopy[57].

It has been reported that the yield of surveillance can be improved by the use of autofluorescence with NBI[36]. According to a study by *Dekker et al,* 52 suspicious lesions were detected in 17 patients using NBI, in comparison to 28 lesions in 13 patients detected with WLE. The pathology of the targeted biopsies revealed neoplasia in 11 patients; neoplasia was detected in 4 patients with both those modalities, in another 4 neoplasia was detected only by use of NBI, and in 3 patients neoplasia was discovered only by WLE, demonstrating non-statistical significance (p= 0.705) for those three modalities. In addition to targeted biopsies, 1522 random biopsies were taken in the context of surveillance. The pathology of these biopsies addedonly 1 patient with dysplasia that remained undetected by both NBI and WLE[34]. A prospective multicenter study by *Leifeld et al* concluded that the two techniques did not differ in the statistical probability of lesion detection, but NBI required less withdrawal time (23 vs 13 min, respectively; P < .001) and biopsy samples (11.9 vs 38.6 biopsy specimens, respectively; P < .001), when compared to WLE[35]. These results are backed by a randomized study by *Ignjatovic et al*, which revealed no difference between the two modalities, regarding the detection of dysplasia[38]. Overall, NBI does not seem to achieve a significantly higher probability of dysplasia detection, compared to conventional HD colonoscopy.

In the same vein *Pellise et al.* conducted a prospective, randomized, controlled trial comparing NBI to DCE in 60 patients with long-standing inactive colonic IBD[58]. The authors reported that NBI was less time-consuming (p<0.01), equally effective in detecting dysplastic lesions and had a lower rate of false-positive biopsies(p=0.001). However, NBI missed suspicious lesions with a non-significant miss rate difference of 30.7% (95% CI, -64.2% to 2.8%).As a result, the study surmised that NBI should not be standard modality for surveillance.

In general, NBI did not substantially differ from DSC, a claim that needs to verified by more robust data pooling. . A possible explanation is that NBI can more readily identify non-neoplastic inflammatory lesions than WLE, which were not pooled in the meta-analysis comparing those techniques[37]. Furthermore, the iterations of NBI are different in those studies, with older generation systems producing suboptimal, darker images[37,42]. Based on the current level of evidence, DCE remains the standard technique for the surveillance in IBD patients

A large randomized prospective study comparing HD-iScan and HD-WLE to standard dye-spraying chromoendoscopy did not prove inferiority for those two techniques, with the question whether i-Scan and HD-WLE will benefit an expert endoscopist remaining unanswered[39]. The authors conclude that they need more multiple-operator studies to assess the helpful potential of these new techniques.

**Confocal laser endomicroscopy**

One of the newest tools in the arsenal of mucosal assessment for dysplasia is the confocal laser endomicroscopy (CLE) that allows in vivo microscopic inspection and evaluation of a targeted lesion in the gastrointestinal tract. This new and evolving method is used in conjunction with HD-WLE and DCE to further define suspicious lesions and assess their histology, by performing real time analysis of the cellular and subcellular characteristics at high resolution. The technique is based on fluorescence, which requires the addition of fluorescein intravenously or topically, but results in high quality images, comparable to traditional histology.

*Kiesslich et al* first used the endoscope-based integrated system in 2007 to demonstrate that neoplastic changes in patients with UC can be identified with very good accuracy (94.7% sensitivity, 98.3% specificity, 97.8% accuracy), compared with standard surveillance endoscopy[59]. Overall, 4.75-fold more neoplastic areas could be identified than with a WLE (p= 0.005), while requiring only half the number of biopsy samples (median 21.2 in the CLE group versus 42.2 undergoing surveillance endoscopy), despite the fact that CLE prolonged colonoscopy by an additional 10 minutes on average (not statistical different; p>0.05). A recent study by *Wanders et al,* for the application of integrated CLE for surveillance in Crohn’s disease, which was terminated early due to critical equipment failure at 4 of the 5 participating centers, came up with a much lower diagnostic yield, with sensitivity of 42.9%, specificity of 92.4% and accuracy of 86.7% [60]. The authors concluded that the technique probably will not be used in the daily practice of screening for CRC in patients with colitis.

A recent study of the probe-based CLE (pCLE) comes from Sweden where it was used for the surveillance of dysplasia in patients with PSC-IBD, a population with 6-fold increase in the incidence of CRC compared with the average risk for CRC population[61]. The study showed good diagnostic accuracy, with the estimated accuracy at 96%, sensitivity at 89% and specificity at 96%, with a low PPV at 41%, but with a very high NPV at 99% for the pCLE. The authors noted that the yield for accuracy fell when assessing areas with mucosal inflammation being misinterpreted as dysplasia. This study challenges the earliest attempts at pCLE systems for CRC surveillance in IBD patients by *van Den Broek et al,* where the authors reported much lower diagnostic yield[62].

**Concluding remarks**

Despite the fact that DCE with targeted biopsies is the gold standard technique for IBD surveillance, it has some limitations. The need for adequate bowel preparation, the long procedure time, and its operator dependence are some of them. Moreover, the presence of active mucosal inflammation or post-inflammatory polyps may affect the images of chromoendoscopy and, in these cases random biopsies are still justified. There are no sufficient data about the effectiveness of the different dyes in detecting dysplasia and there are some concerns about methylene blue inducing DNA damage but have not yet been validated. Two recent editorials have questioned the SCENIC consensus, because chromoendoscopy and targeted biopsies have not been shown to improve colorectal cancer mortality[63,64].Even when accounting for those limitations, chromoendoscopy remains a validated technique that becomes more and more recommended for CRC surveillance in IBD patients, whilst white light endoscopy with random biopsies should only be performed when the skill or the equipment for chromoendoscocpy is unavailable

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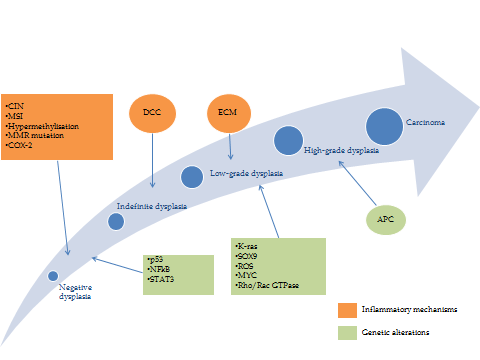
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**Table 1 CRC risk factors and surveillance**

**CRC**, Colorectal cancer; **CD**, Crohn’s disease; **PSC**, Primary sclerosing cholangitis; **UC**, Ulcerative colitis

**Figure 1 Colitis-associated colon cancer sequelae**



**COX-2**, cyclooxygenase-2; **ECM**, extra-cellular matrix; **MMR**, mismatch repair mutation; **DCC**, deleted in colorectal carcinoma; **APC**, adenomatous polyposis coli; **MSI**, microsatellite instability; **CIN**, chromosomal instability; **ROS**, reactive oxygen species; **K-ras**, Kirsten rat sarcoma 2 viral oncogene homolog; **p53**, tumor protein p53; **NF-kB**, nuclear factor kappa-light-chain-enhancer of activated B cells; **STAT3**, signal transducer and activator of transcription 3; **SOX9**, SRY-box 9 gene

**Figure 2 Algorithm for CRC surveillance in IBD patients**

