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Endoscopic Surveillance in Longstanding Colitis

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Keywords

Inflammatory bowel disease; surveillance; chromoendoscopy; colorectal cancer; dysplasia; random biopsy

Introduction:

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract whereby long standing inflammation leads to an increase in the relative risk of colorectal cancer. Based on a meta-analysis of population-based studies, the relative risk of colorectal cancer in ulcerative colitis (UC) as compared to the general population is 2.4, and the risk is similar in Crohn's disease (CD).[1,2] The risk factors for colorectal cancer that are specific to IBD include the duration, extent and severity of inflammation as well as concomitant primary sclerosing cholangitis (PSC), strictures, pseudopolyps, and personal history of dysplasia.[3] Patients with ulcerative proctitis do not have an elevated risk of colorectal cancer.[4] The declining rates of colon cancer in IBD may be related to improved medical management of IBD and implementation of colon cancer surveillance.[5]

Surveillance in Inflammatory Bowel Diseases: Current Guidelines

Based on the relative increase in colorectal cancer in IBD as compared to the general population, multiple societies have recommended surveillance for dysplasia and colon cancer in patients with left sided or extensive ulcerative colitis and Crohn's disease affecting >1/3 of the colon starting 8 to 10 years after diagnosis. In patients with concomitant PSC, surveillance is initiated at the time of diagnosis.[6–8] Historically, dysplasia in IBD was presumed to be invisible, and surveillance entailed colonoscopy with 4-quadrant random biopsies every 10 cm in the colon with the goal of obtaining at least 33 biopsies to achieve a sensitivity of 90% to detect dysplasia, if present.[9] However, there are significant limitations to this approach including the time-intensive nature of obtaining large number of biopsies,

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significant pathology fees, and limited sensitivity. The method of using random biopsies for surveillance has been further challenged with the advent of improved imaging techniques to evaluate the colon, including high definition endoscopes as well as chromoendoscopy, which demonstrate that dysplasia in IBD is endoscopically visible.

The Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients (SCENIC) International Consensus Statement recommended the routine use of high definition colonoscopy and chromoendoscopy for surveillance exams. Chromoendoscopy as compared to standard white light endoscopy led to a 15% increase in the overall dysplasia detection rate and a 51% increase in the detection of endoscopically visible dysplasia, and compared to high definition white light colonoscopy led to a 12% increase in the overall dysplasia detection rate.[10–17]

Assessing the Evolving Evidence Since SCENIC

The SCENIC recommendation to use chromoendoscopy for dysplasia detection in IBD surveillance was based on a meta-analysis of 8 studies, including 2 randomized and 4 tandem studies comparing standard white light endoscopy and chromoendoscopy, and a tandem study evaluating high definition white light[18]. Several studies have been published following the SCENIC statement (Table 1). Most recently, Marion et al[19] showed that chromoendoscopy with methylene blue was superior to white light endoscopy for detecting lesions (OR 2.4; 95% CI, 1.4–4.0, p = 0.001) in a prospective longitudinal cohort of 68 patients with UC and Crohn's disease requiring surveillance over a 28 month period. Importantly, they found that a negative result from a chromoendoscopy examination was the best indicator of a dysplasia-free outcome. In a larger multicenter cohort study, Carballal et al[20] examined the real-life use of chromoendoscopy for surveillance in 350 patients where segments were examined first with white light endoscopy then chromoendoscopy. The incremental dysplasia yield using chromoendoscopy was 57.4% as compared to standard and high definition colonoscopy.

It is important to recognize that a second look will increase the yield of any examination, and thus, the tandem design in these studies may introduce operator bias. Two recent studies whereby the colonoscopies were performed at different time intervals provide additional support for the argument of an increased dysplastic yield of chromoendoscopy exams compared to white light exams. Deepak et al[21] estimated the rate of missed dysplastic lesions with white light endoscopy by comparing the findings of an index colonoscopy and subsequent chromoendoscopy that was performed a median of 6 months later. Of 95 patients with a diagnosis of dysplasia, chromoendoscopy identified visible lesions in 50 patients, including 34 lesions not previously identified. Among the 40 patients with dysplasia from random biopsies, previously called invisible dysplasia, 30% were found to have visible lesions with chromoendoscopy. Successful identification of lesions allowed endoscopic resection of 43 lesions. In a second retrospective analysis, Rubin et al[22] described 85 dysplastic lesions in 53 patients who were referred to a tertiary care center where additional colonoscopies were performed using HD colonoscopy with or without chromoendoscopy. Using chromoendoscopy, they identified at average of 0.32 more lesions per endoscopy that may have previously been described as invisible dysplasia. Overall, these studies describing

identification of dysplastic lesions with chromoendoscopy demonstrate that “invisible” dysplastic lesions can be seen with the appropriate expertise and technique.

A recent meta-analysis included 10 randomized controlled trials comparing chromoendoscopy with other endoscopic modalities for dysplasia surveillance in IBD. Three studies compared chromoendoscopy and standard definition WLE, 3 abstracts[23,24,25] compared chromoendoscopy and HD-WLE, and four trials compared chromoendoscopy and narrow band imaging. Overall, there was a greater chance of identifying dysplasia with chromoendoscopy as compared to all other techniques (RR of 1.37 with 95% CI 1.15–3.91); however, this effect was only seen in the sub-group analysis comparing standard WLE and chromoendoscopy, not with comparisons to HD-WLE or narrow band imaging.[26]

Alternative Surveillance Techniques

The SCENIC guidelines evaluated alternative surveillance techniques available for dysplasia surveillance in inflammatory bowel disease, including narrow band imaging (NBI) and autofluorescence, and did not recommend routine use of either of these technologies. NBI is an imaging-enhancement technique relying upon use of specific wavelengths of blue and green light. There were three randomized studies included in the SCENIC analysis: one randomized-cross over study comparing NBI to white light colonoscopy[27] and two randomized trials comparing NBI to chromoendoscopy[28,29], and none of the studies showed a benefit from NBI in dysplasia detection as compared to the alternative surveillance techniques.

Full spectrum endoscopy (FUSE), which incorporates wide angle screen to enhance visualization, specifically behind folds, was an appealing technique to evaluate for dysplasia in IBD. Leong et al[30] performed a randomized, tandem cross-over study in 52 patients with IBD patients and found that the miss rate was much higher using forward viewing colonoscopy at 71.4% as compared to FUSE which had a miss rate of 25.0% per lesion. The study had a small sample size, and the overall dysplasia rate was 36.5%, which is much higher than estimated by other studies. Most notably, the miss rates were calculated based on the insertion and withdrawal from the first technique as compared to insertion exam of the second technique, and chromoendoscopy was performed during the second withdrawal. Ultimately, the study showed significant miss rates using both techniques, underscoring the limitations of high definition white light endoscopy where 56% of patients with dysplasia required chromoendoscopy for detection. Though FUSE has the potential to augment visualization, it does not appear to be an adequate alternative for chromoendoscopy.

Natural History of Dysplastic Lesions in IBD

Understanding the natural history of dysplastic lesions in IBD, particularly in lesions detected by newer endoscopic techniques such as chromoendoscopy, will inform our approach to endoscopic surveillance. As previously discussed, the study by Marion et al demonstrated that a negative result from a chromoendoscopy examination was the best indicator of a dysplasia-free outcome.[19] In a retrospective study, Choi et al[31] evaluated the natural history of low grade dysplasia detected between 1993 and 2012 and determined risk

factors for progression of low grade dysplasia by following 172 patients for a median of 48 months. Macroscopically non-polypoid lesions, invisible dysplasia, ≥1 cm lesions, and history of biopsies that were indefinite for dysplasia were significant risk factors for progression to high grade dysplasia or colorectal cancer. The rate of progression to high grade dysplasia or colon cancer was estimated at 10.9% at 1 year and 13.6% at 2 years after diagnosis of low grade dysplasia.

Similarly, Ten Hove et al[32] retrospectively examined the natural history of dysplastic lesions in IBD in 159 patients who were diagnosed with low grade dysplasia from 2000 to 2014 based on targeted or random biopsies and enrolled in a surveillance program utilizing the guidelines from the British Society of Gastroenterology. With a median follow up 4.7 years, the overall incidence rate of an advanced neoplasia was 1.34 cases per 100 patient-years for low grade lesions detected on targeted and random biopsies and 2.29 cases per 100 patient-years in lesions detected on random biopsies. Though patients who underwent colectomy for management of low grade dysplasia were excluded, the rate of progression was lower than previously described[33] and may reflect a new era of endoscopically-resectable lesions with lower overall incidence of colon cancer. The median time to advanced neoplasia was 3.3 years, providing some reassurance in terms of the rates of dysplasia progression, and there were no significant differences in the natural history of the dysplasia detected using white light endoscopy as compared to chromoendoscopy. While it's challenging to reconcile the different estimates of the natural history of low grade dysplasia, the latter study included dysplasia diagnosed starting in 2000 and may represent a more accurate estimate in the video endoscope era. In spite of improved techniques to enhance detection and removal of visible lesions during endoscopy, there has not been an associated increase in the rate of colectomy.[5]

Random versus Targeted Biopsies

The Majority of Dysplasia is Visible

The utility of random biopsies was, in part, predicated on the notion that invisible dysplasia is common in IBD; however, with the improvement in endoscopic equipment with high definition and chromoendoscopy, most dysplasia is understood to be visible and able to be identified with a careful examination and targeted biopsies. Rutter et al[34] showed that using white light endoscopy at an IBD referral center, 90% of dysplasia was visible with surveillance colonoscopy. The SCENIC guidelines adapted the Paris Classification system and defined common terminology to describe dysplasia in IBD with an emphasis on determining whether a lesion could be resected endoscopically. The lesions are classified as visible or invisible. Visible lesions can be further characterized based on whether they protrude into the lumen by 2.5 mm or more. Polypoid lesions which protrude by 2.5 mm or more into the lumen can be further described as sessile or pedunculated, and non-polypoid lesions can be described as superficial elevation (<2.5 mm above the lumen), flat, or depressed lesions. In addition, the presence or absence of a distinct border is a critical feature to describe in order to assess whether complete endoscopic resection may be possible. Based on the appreciation that most dysplasia is visible, the SCENIC guidelines recommend that patients with endoscopically invisible dysplasia should be referred to an

endoscopist with expertise in IBD and should undergo evaluation with high definition colonoscopy with chromoendoscopy to assess for visible dysplasia.[35]

The Clinical Role of Random Biopsy

There has been an evolving appreciation that the yield from random colon biopsies in IBD is quite low,[17,36] and time spent taking these random biopsies may be better spent examining the colon and obtaining biopsies from areas that appear abnormal. Among patients with dysplasia undergoing high-definition white-light colonoscopy or chromoendoscopy reviewed in the SCENIC guidelines, dysplasia is detected only on random biopsies in approximately 10% of patients and on targeted biopsies in the other 90%. About 1% to 1.5% of all patients undergoing surveillance had dysplasia detected by random biopsy. Out of 48,522 random biopsies from 1635 patients that were performed in 11 chromoendoscopy studies, dysplasia was identified in 45 (0.09%) biopsy samples.[35]

Nonetheless, many clinicians still obtain random biopsies regardless of the method used for surveillance. Recent studies continue to show the low yield of random biopsies in surveillance in IBD. In 924 random surveillance biopsies from 28 patients with long standing UC, none of the biopsies showed evidence of dysplasia, and only 0.7% were indefinite for dysplasia.[37] A second retrospective study by Gasia et al[38] compared the neoplasia detection rate using random versus targeted biopsies using different endoscopic methods, including white light endoscopy, high definition colonoscopy, virtual chromoendoscopy, and dye chromoendoscopy. The neoplasia detection rate was 19% in the targeted versus 8% in the random biopsy group when including the different endoscopic techniques used overall (p-value of <0.001).

The most compelling evidence though comes from a recently published randomized trial that directly compared dysplasia detection strategies, using random versus targeted biopsies. Watanabe et al[39] randomized 246 patients with ulcerative colitis for at least 7 years to colonoscopy with random biopsies every 10 cm or targeted biopsies from suspicious areas concerning for neoplasia. While the number of participants was not sufficient to power a non-inferiority study, the study compared the two biopsy strategies and suggested that use of targeted over random biopsies was superior. They found a greater number of biopsies were obtained in the random versus targeted biopsy group (34.8 versus 3.1), and a longer duration of time was spent performing the colonoscopy in the random versus target biopsy group (42 v. 27 minutes, p-value <0.001). In spite of the greater number of biopsies and examination time, the mean number of biopsies containing neoplasia was higher in the targeted biopsy as compared to random biopsy group (0.211 versus 0.168), which was not statistically significant. More patients in the targeted (10.5%) as compared to the random (3.7%) biopsy group were diagnosed with neoplasia, p = 0.052. There was also a strong association between prior or current inflammation and dysplasia, such that dysplasia was only detected in random biopsies in areas with current or prior inflammation.

In a prospective study of 1000 patients with IBD undergoing surveillance in France, Moussata et al[40] evaluated chromoendoscopy with random biopsies and demonstrated that chromoendoscopy with targeted biopsies detected the majority of patients with dysplasia, and only 15% of patients with neoplasia were identified from random biopsies. Detection of

neoplasia in random biopsy was associated with a personal history of neoplasia, tubular appearing colon, and presence of primary sclerosing cholangitis. The findings help define risk factors to stratify patients into those who may benefit from random biopsies in addition to chromoendoscopy-targeted biopsies. They also provide a starting point for reducing the use of non-targeted biopsies, especially in normal appearing colons.

Implementation of Chromoendoscopy

Implementation of chromoendoscopy into clinical practice remains an important issue facing providers with multiple potential barriers. However, the evidence supporting the efficacy and cost-effectiveness of chromoendoscopy for surveillance should provide impetus for practices to work through potential challenges. Clinical questions on the role of random biopsy and the natural history of IBD dysplasia, and practical issues, such as learning a new technique, access to dye during a time of shortage and price increases, obtaining reimbursement, and benchmarking quality have presented barriers to widespread adaption. Sanduleanu et al[41] provide a practical roadmap to introducing chromoendoscopy into practice, which starts with obtaining the appropriate equipment and becoming familiar with the chromoendoscopy protocol and procedures and terminology. Quality measures for IBD surveillance need to be developed to provide meaningful indications of performance that can be linked to reimbursement.

Importantly, on-line video and atlas teaching materials on the optimal surveillance strategy technique, such as chromoendoscopy with targeted biopsy are available. The ability to teach and implement chromoendoscopy effectively and provide potential tools to help identification of endoscopic features of dysplasia has been shown. Picco et al[18] examined whether six endoscopists without experience in chromoendoscopy could effectively learn the new technique. Using pictures of lesions, there was high interobserver agreement about which lesions were dysplastic and non-dysplastic. While procedure times were longer for chromoendoscopy, with minimal experience withdrawal time decreased. With the practice of as few as 5 procedures, withdrawal time was reduced by an average of 13 minutes, demonstrating the rapid uptake of chromoendoscopy by endoscopists. A subsequent multi-center cohort study demonstrated that chromoendoscopy can be successfully implemented into different clinical practices. Carballal et al[20] introduced chromoendoscopy into academic and local community centers with endoscopists with a wide range of experience with chromoendoscopy. While there was incremental dysplasia detection from chromoendoscopy, the dysplasia detection rates were similar regardless of prior experience with chromoendoscopy, and there was no significant learning curve based on comparisons of dysplasia detection rates in the first one-third versus last one-third of colonoscopies performed by an individual.

Ongoing questions may arise about the utility and cost-effectiveness of routine colonoscopy with random biopsies or chromoendoscopy with surveillance in IBD given the declining rates of colon cancer. Using Markov modeling, the cost effectiveness of chromoendoscopy targeted biopsies was compared to colonoscopy with random biopsies and no surveillance for colon cancer in UC patients. Chromoendoscopy with targeted biopsies was found to be not only more effective but also less costly than white light endoscopy at all modeled

surveillance intervals though chromoendoscopy is only cost effective as compared to no surveillance when performed at 7-year intervals.[42]

Prospective longitudinal studies of colonoscopy surveillance will be needed to monitor the rate of interval cancers, need for surgery and mortality, and cost effectiveness with new surveillance programs; and ultimately, allow the risk stratification of patients to the most appropriate surveillance intervals. While we await such high level trials, and we continue to routinely perform surveillance, it is important to use the currently shown optimal method.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Opinion Statement:

There is a relative increase in the risk of colon cancer in patients with inflammatory bowel disease (IBD) affecting the colon, and endoscopic surveillance is advocated to mitigate this risk. The current standard practice is to survey this high-risk patient population using colonoscopy. Chromoendoscopy with targeted biopsies has emerged as the colonoscopy modality recommended by the major societies to optimize dysplasia detection. Studies over the past year support the improved yield from targeted as compared to random biopsies and improved dysplasia detection from chromoendoscopy as compared to white light endoscopy. Ongoing efforts should focus on the implementation of chromoendoscopy as the primary modality for colorectal cancer surveillance in IBD. Our review will describe current status and provide an update on the recent literature on surveillance colonoscopy in patients with IBD.

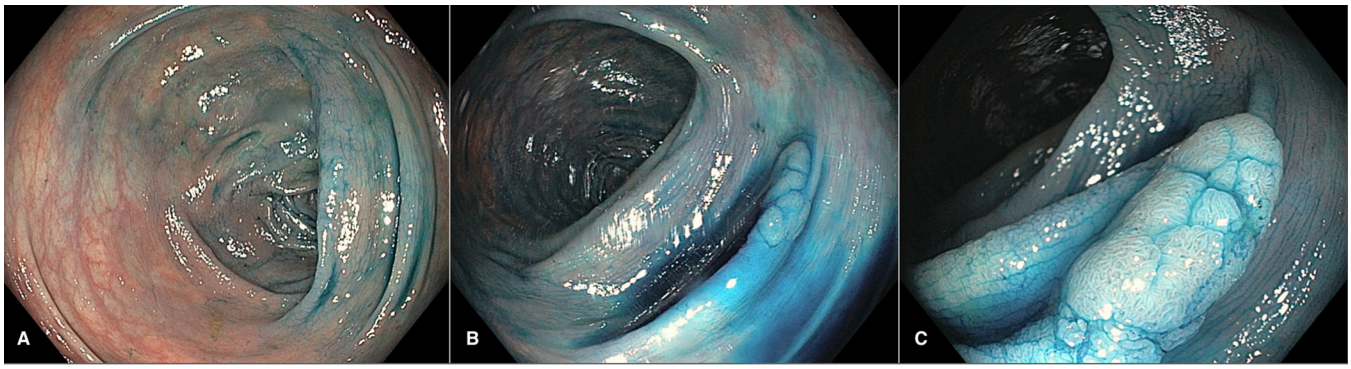

Fig. 1.

Chromoendoscopy in IBD surveillance. a The dye is applied during withdrawal for dysplasia detection. b The innominate grooves can easily be seen with the application of the dye. Interruption of the grooves highlights a flat lesion. c Closer view of the lesion shows a non-polypoid superficially elevated 1 cm lesion with a discrete border that appears endoscopically resectable.

Table 1.

Studies published after the SCENIC statement

Status	Topic	Year Published	Author	Country	Title	Study Period	Study Design	Comparison	Cohort	Dysplastic Lesions	High Definition	Outcome for Dysplasia Detection	Ref
PUBLISHED	Chromoervdoscopy targeted	2017	Leong	Australia	Full-spectrum Endoscopy Improves Surveillance for Dysplasia in Patients With Inflammatory Bowel Diseases	Feb 2014-Dec 2015	Prospective, randomized crossover tandem	FUSE	Surveillance	31%%	yes	Chromoendoscopy Superior	30
	Chromoendoscopy targeted	2016	Carballal	spain	Real-life chromoendoscopy for neoplasia detection and characterisation in long-lasting IBD	June 2012–2014	Prospective, multicentre cohort	HD	Surveillance	16%	yes (585%)	Superior	20
	Chromoendoscopy targeted	2016	Gasia	Canada	Targeted Biopsies identify Larger Proportions of Patients with Colonic Neoplasia Undergoing High-Defmitton Colonoscopy, Dye Chromo endoscopy, or Electronic Virtual Chromoendoscopy	Apr 2011-Mar 2014	Retrospective	HD, virtual CE	Surveillance		yes	Superior*	38
	Chromoendoscopy targeted	2016	Rubin	USA	Outcomes of Colitis-Associated Dysplasia After Referral from the Community to a Tertiary Center	2008–3015	Retrospective	n/a	Dysplasia referral	n/a	yes	Superior	22
	Chromoendoscopy targeted	2016	Marion	USA	Chromoendoscopy is More Effecttvethan Standard Colonoscopy in Detecting Dysplasia During Long-Term Surveillance of Patients with Colitis	Sept 2005–0 ct 2011	Prospective, longitudinal	WLE	Surveillance	12%	no	Superior	19
	Chromoendoscopy targeted	2016	Deepak	USA	Incremental diagnostic yield of chromoendoscopy and outcomes in inflammatory bowel disease patients with a history of colorectal dysplasia on white-light endoscopy	Jan 2006-Aug 2013	Retrospective	HD	Dysplasia referral	n/a	yes	Superior	21
	Chrom oe ndoscopy targeted	2015	Choi	UK	Forty-Year Analysis of Colonoscopic Surveillance Program for Neoplasia in Iterative Colitis: An Updated Overview	2013? Data taken from Surveillance nee program active over 40year period	Retrospective	WLE	Surveillance	24%	no	Superior	31
	Chrom oendoscopy targeted	2015	Mooiweer	Netherlands	Chromoendoscopy for Surveillance in Inflammatory Bowel Disease Does not Increase Neoplasia Detection Compared with Conventional Colonoscopy with Random Biopsies: Results from a Large Retrospective Study	2000–2013	NO	WLE	Surveillance	11%	yes (subset)	No difference	additional reference 1
	Endomicroscopy	2016	Wanders	Belgium	Limited applicability of chromoendoscopy-guided confocal laser endomicroscopy as daily-practice surveillance strategy in Crohn's disease	2010–2014	Multicenter, prospective, cohort	CE	Surveillance lerohns}	10%	yes	Endomicroscopy endomicroscopy has high specificity, not practical	additlonal reference 2
	Endomicroscopy	2014	Freire	Portugal	Surveillance in Ulcer attve Colitis: Is chromoendoscopy-guided Endomicroscopy Always Better than Conventional Colonoscopy? A Randomized Trial	2011–2013	Prospective randomized	HD	Surveillance	7%	yes	endomicroscopy does not increase dysplasia yield NBI	additlonal reference 3
	NBI	2015	Leifeld	Germany	White-Light or Narrow-Band Imaging Colonoscopy in Surveillance of Ulcerattve Colitis: A Prospective Study	2007–2012	Multicenter prospective randomized tandem	WLE	Surveillance	23%	no	Not superior	additlonal reference 4
ABSTRACTS	Chromo - Iscan	2017	Lopez-Serrano	Spain	Virtual chromoendoscopy with I-Scan as alternative to dye-spray chromoendsocopy for dyspatsia detection in long standing colonic inflammatory bowel disease	Jan 2013-Sept 2016	Rrospecttve	i-Scan	Surveillance	13.60%	yes	C hromoendoscopy l-Scan not inferior to CE	additional reference 5
	Chromo - HD	2017	Jung	Korea	High-Definition White-Light Endoscopy Versus High-Deftnition Chromoendoscopy in Detecttonof Dysplasia in Long-Standing Ulcerative Colitis: A Multicenter Prospective Randomized Controlled Study		Prospective	HD	Surveillance	16%	yes	Nodifference	additlonal reference 6
	Chromo - HD	2016	Paul	USA	Chromoendoscopy with High Deftnitlon White Light Endoscopy for Colorectal Cancer Surveillance in IBD: Experience from a Community Medical Center	July 2015 - Aug 2016	Prospective	none	Surveillance	61%	yes	Superior	additlonal reference 7
	Chromo - SD	2016	Pelitari	UK	Colonoscopy Surveillance in Long Standing mflammatory Bowel Disease in a General District Hospital and Comparison Between White Light Endoscopy and Chromoendoscopy in Detecting Dysplasia During Surve Dlance		Retrospective	WLE	Surveillance		not stated	Superior	additional reference 8
	Chromo - HD	2016	lacucci	Canada	Final results of a randomised study com par inghlgh-definltion colonoscopy alone with high- deflniteion dye spraying and electronic visual chromoendoscopy using iSCAN for detection of colonic neoplastic lesions during IBD sutvedlanc ecolonoscopy		Randomized	HD and iSCAN	Surveillance	28%	yes	No difference	25
	Chromo - HD	2016	Park	Korea	High definition chromoendoscopy with water-jet versus high deft nitlon white light endoscopy m the detection of dysplasia in long		Randomized	HD	Surveillance	2.00%	yes	No difference	24

Status	Topic	Year Published	Author	Country	Title	Study Period	Study Design	Comparison	Cohort	Dysplastic Lesions	High Definition	Outcome for Dysplasia Detection	Ref
					standing ulcerattvecolitis: a multicenter prospective randomized controlled study								
	Chromo - HD	2015	Mohammed	UK	High Definition white light endoscopy (HDWLE) versus high definition with chromoendoscopy (HDCE}m the detection of dysplasia in long standing ulcerative colitis: A Randomized Controlled Trial		Randomized	HD	Surveillance	16%	yes	Superior	23
	Chromo - SD	2014	Java id	UK	The Utility of Routine Chromoendoscopy for Detection of Dysplastic Lesions During Surveillance Colonoscopy in Patients with Colonic Inflammatory Bowel Disease. Does Research Translate to clinical Practice?	Jan 2012-Dec 2013	Retrospective	WLE	Surveillance	22%	no	Superior	additional reference 9
	NBI - HD	2016	Watanabe	Japan	Comparison between newly developed narrowband imaging and panchromoendoscopy for surveillance colonoscopy in patients with ulcerattve colitis: a prospective multicentre randomised controlled trial, navigator study		Randomized	HDCE	Surveillance	15%	yes	No difference	additional reference 10

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