The Detection of Nonpolypoid (Flat and Depressed) Colorectal Neoplasms in Patients With Inflammatory Bowel Disease

ROY SOETIKNO,[1] VENKATARAMAN SUBRAMANIAN,[2] TONYA KALTENBACH,[1] ROBERT V. ROUSE,[1] SILVIA SANDULEANU,[3] NORIKO SUZUKI,[4] SHINJI TANAKA,[5] and KENNETH McQUAID[6]

[1]VA Palo Alto and Stanford University, Palo Alto, California; [2]St James University Hospital, University of Leeds, Leeds, United Kingdom, [3]University of Maastricht Medical Center, Maastricht, The Netherlands, [4]St. Marks Hospital, London, United Kingdom; [5]University of Hiroshima, Hiroshima, Japan; and [6]VA San Francisco and the University of California San Francisco

Random biopsy is recommended in the US to detect flat dysplasia in patients with colonic inflammatory bowel disease (cIBD),[1] despite its known poor sensitivity and the significant risk of missing flat dysplasia. Herein, we describe pancolonic chromoendoscopy (CE)[2] using indigo carmine (Akorn, Inc, Lake Forest, IL) with targeted biopsy which is proven to be more sensitive for detecting flat dysplasia in cIBD.[3–5]

Description of Technology

The entire mucosa should be free from pus, mucus, or stool. Screening should be performed when cIBD is inactive and the bowel is clean.[2] During withdrawal, we spray diluted indigo carmine (~0.03%) circumferentially through the water jet channel using a pump (Video). We look for nodular or villous areas, slight elevation or depression, tissue friability, obscure vascular pattern, or discoloration (uneven redness). Upon visualizing a possible lesion, we spray concentrated indigo carmine (~0.13%) using a 60mL syringe through the working channel to delineate its border, contour, and mucosal pattern (Table 1). We resect the lesion, if appropriate, and biopsy other lesions, suspicious areas, or poorly visualized (due to inflammation) segments (Figure 1). We emphasize that recognition of nonpolypoid lesions requires training.

Supporting Data

Meta-analysis of clinical studies supports the strategy of CE with targeted biopsy over that of white light endoscopy with random biopsy (Supplementary Materials and Methods) for surveillance. CE yielded a 7% increase in the detection of any dysplasia (Table 1). Moreover, when using CE with targeted biopsy compared to white light endoscopy with random biopsy, the likelihood to detect any dysplasia was 8.9 times higher, to detect nonpolypoid dysplasia was 5.2 times higher, and to miss dysplasia was 93% lower (Table 1). The number needed to test using CE in order to detect an additional patient with dysplasia was 14.

CE is inexpensive (a 5 mL vial is $7.00) (Table 2). It requires a modest increase in procedure time (approximately 11 minutes). Notably, the time reported from the studies also included random biopsies, which are not recommended with CE due to the very low yield. Thus, the procedure time of the recommended procedure, CE with targeted biopsy,[3,6] is likely shorter than reported.

A number of randomized clinical trials evaluated the use of narrow band imaging in lieu of CE and found no benefit.

Rationale

Our rationale for the use of CE and algorithm for the management of detected lesions follows:

Indigo carmine is useful to highlight areas suspected to contain nonpolypoid lesions.[7] It pools into mucosal surface crevices and outlines subtleties in elevation or depression. It accentuates the mucosal pattern by filling colorectal gland pits. Spraying diluted indigo carmine assists in defining the extent of colitis. Neoplasms located in the colon uninvolved by colitis are considered sporadic and managed as such. In the involved segments, the transparent blue solution assists in identifying areas suspicious for nonpolypoid lesions. Concentrated indigo carmine is useful to delineate the border and surface of suspected and obvious lesions. It can be useful to gain insight into the likely pathology (inflammation, hyperplastic, serrated, adenoma/low and high-grade dysplasia, or invasive carcinoma).

The 3 subtypes of nonpolypoid lesions (superficial elevated, flat, and depressed) often contain advanced pa-

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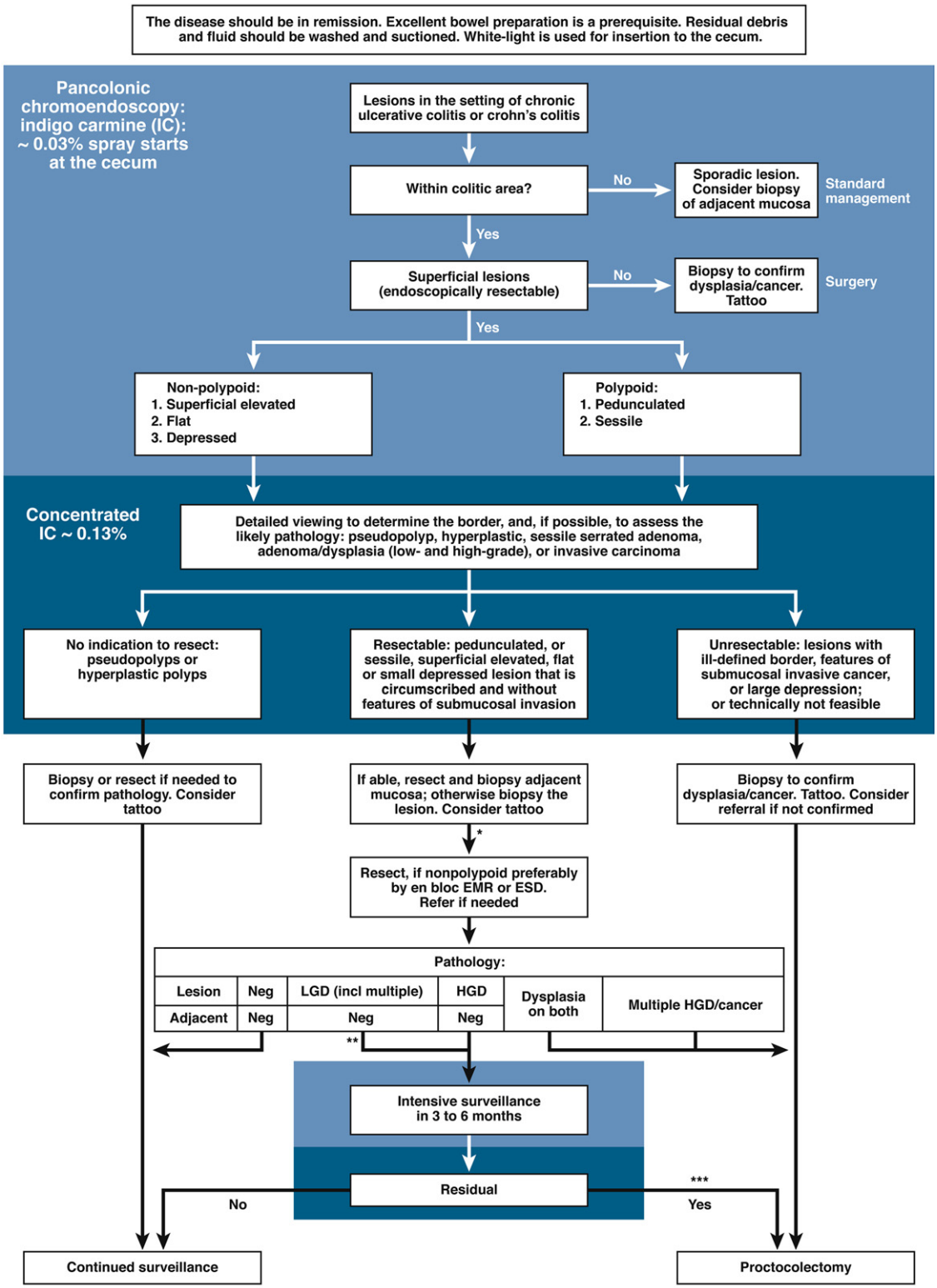
Algorithm of pancolonic chromoendoscopy and targeted biopsy, and management of detected superficial colorectal lesions



Mucosal inflammation and multiple pseudopolyps may affect the interpretation of chromoendoscopy. Random biopsy is still justified in these circumstances.
* The resection of circumscribed nonpolypoid lesion is colonic IBD requires a high level of expertise - referral may be necessary.
** The pathology of LGD may require confirmation by a gastrointestinal pathologist.
*** Repeat resection may be considered for small residual lesions.

Table 1. Summary of Meta-analysis of Chromoendoscopy (CE) With Targeted Biopsy, Compared With White Light Endoscopy (WLE) With Random Biopsy, for Surveillance Colonoscopy in Patients With Colonic Inflammatory Bowel Disease

Outcomes	Number of studies/patients	Method of analysis	Results of meta-analysis
Comparison of number of patients with dysplasia	6/665	Incremental yield (IY) of CE with targeted vs WLE with random for detection of dysplasia/patient	IY = 7%; 95% CI, 3.3–10.3%
Number needed to treat	6/665	Inverse of IY	NNT = 14.3; 95% CI, 9.7 to 30.3
Dysplastic lesions	6/665	Compare rate of dysplasia detected using CE with targeted biopsy vs WLE with targeted biopsy	Odds ratio = 8.9; 95% CI, 3.4–23.0
Flat dysplastic lesions	4/518	Compare rate of dysplasia diagnosed from targeted biopsy during CE vs that during targeted biopsy with WLE	Odds ratio = 5.2; 95% CI, 1.7–15.9
Miss rate[a]	5/565	Compare rate of dysplasia detected during random biopsy performed during CE vs that of random biopsy with WLE, and lesions missed by WLE but detected by CE	Odds ratio = 0.07; 95% CI, 0.03–0.21
Procedure time	4/520	Compare difference in mean procedure time.[b]	Mean difference = 10.9 minutes; 95% CI, 9.1–12.6

CE, Chromoendoscopy; IY, incremental yield; NNT, number needed to treat; WLE, white light endoscopy.
[a]Miss Rate was defined as dysplastic lesions detected by random biopsy alone or by the alternative modality (ie, lesions that were missed by WLE but detected by CE) in studies with a tandem colonoscopy design and by random biopsy alone in studies with separate CE and WLE arms. For detail of the meta-analysis, please see Supplementary Materials and Methods.
[b]Procedure times of CE and WLE included time to perform targeted and random biopsy.

thology, and are more readily visible after indigo carmine spray. When in doubt, targeted biopsies should be performed to distinguish nonpolypoid dysplastic lesions from inflamed or scarred mucosa. The adjacent mucosa should be carefully examined to detect more extensive neoplastic involvement. Biopsy should be obtained to exclude dysplasia that may not be visually recognized in the adjacent mucosa. The finding of a stricture in patients with chronic ulcerative colitis raises concern for underlying carcinoma. Because biopsy may be falsely negative, surgery should be considered.

The nonpolypoid configuration of the lesions can be difficult to recognize on histology. This is largely because of the specimen contraction and distortion that occurs between resection and fixation producing a false polypoid appearance. The endoscopist needs to describe the macroscopic finding and may need to flatten and orient the resected specimen.

On histology, the spectrum of pathology is vast and unique. Pseudopolyps and hyperplastic lesions are benign. Sessile serrated adenomas have been newly described.[8] Neoplastic change can be identified in lesions that range from polypoid adenomas to flat adenomas and even to "invisible" dysplasia in adjacent mucosa. The diagnosis of high-grade dysplasia has high concordance among pathologists, while low-grade dysplasia (other than the conventional adenomas) has only fair concordance; accordingly, a review by a GI pathologist may be necessary. Cancers in ulcerative colitis often have villous features or contain signet ring cells. They may not follow the adenoma-carcinoma sequence—6% of these cancers are reported to be small flat invasive carcinomas without adjacent adenomas.[8]

Video Description

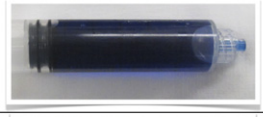
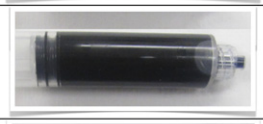
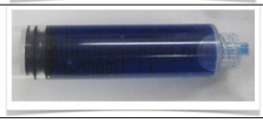
We describe the technique of CE with targeted biopsy and provide examples of nonpolypoid dysplasia in cIBD.

Take Home Message

In the previous era of fiber optic endoscopy, visualization of lesions in patients with IBD was limited. In that era, the term dysplasia associated lesion or mass (DALM) was coined for polypoid or mass lesions, and nonpolypoid neoplasms were impossible to visualize. Thus, the random biopsy technique was recommended in an attempt to detect "invisible" dysplasia, which predicted an increased risk of undetected cancers. That era has passed. Today, high-resolution video system with CE

Figure 1. Algorithm of pancolonic chromoendoscopy and targeted biopsy, and management of detected superficial colorectal lesions. For lesion detection we spray diluted indigo carmine solution using a water jet. For diagnosis, we spray concentrated solution through the working channel directly on the lesion. Others use a specialized spray catheter, to apply concentrated solution for detection and diagnosis. Factors such as patient age and comorbid conditions and the skills of the treating endoscopist, pathologist and surgeon should be incorporated into decision-making. Lesions with low-grade (LGD) or high-grade dysplasia (HGD) may be managed with endoscopic resection alone provided that the lesion is circumscribed, limited to the mucosa, can be resected completely, and is without dysplasia in the immediate surrounding area.

Table 2. Concentration of Indigo Carmine Solutions Used During Colonoscopy

Purpose of Indigo Carmine Solution	Mixture	Depth of blue
Detection of Nonpolypoid Colorectal Neoplasms IBD	2 Ampules with 250cc of water (0.03%)	
Evaluation of possible or definite lesions	1 Ampule with 25cc of water (0.13%)	
Submucosal injection	10 Drops with 100cc of saline	

enables us to directly visualize, localize, and diagnose nonpolypoid lesions.

In our algorithm, the term DALM plays no role. Its use in practice and publications is inconsistent, leading to confusion. Instead, we employ standardized terms: polypoid/nonpolypoid, low/high grade dysplasia and resectable/non-resectable. As we adopt the new technique and algorithm, we emphasize the heightened vigilance required for surveillance colonoscopy of patients with cIBD where inflammation and/or scarring may obscure lesion detection. CE highlights the areas that warrant more attention, provides the contrast necessary to view them in greater detail, and the findings before targeting for biopsy or resection (Table 2). The training provided here allows all readers to develop expertise with this technique.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2013.04.008.

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Reprint requests

Address requests for reprints to: Roy Soetikno, MD, Gastrointestinal Endoscopy Unit, VA Palo, 3801 Miranda Ave, GI111, Palo Alto, California 94304. e-mail: soetikno@earthlink.net; fax: 650-849-0255.

Conflicts of interest

The authors disclose no conflicts.

Supplementary Materials and Methods

We searched electronic databases including PubMed (1965-January 2013), Embase (1974-January 2013) and Ovid (1965-January 2013), Cumulative Index to nursing and allied health (CINAHL, 1982-January 2013), Ingenta (1991-January 2013), using the search terms *chromoendoscopy or chromoscopy or dye spraying*, and *ulcerative colitis or inflammatory bowel disease*. In addition, we hand searched the reference lists of all articles selected from the electronic database search.

We included publications in any language that met the following criteria: the study included patients with chronic ulcerative colitis or colonic Crohn's disease undergoing surveillance colonoscopy, and the study compared chromoendoscopy (CE) with targeted biopsy vs standard white light endoscopy (WLE) with random biopsy. We analyzed studies with sufficient information to calculate the yield of dysplasia and 95% confidence interval (CI).

We assessed the quality of the studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool.[1] We performed a meta-analysis of CE with targeted biopsy compared to WLE with random biopsy to assess the incremental yield of detecting patients with any dysplastic lesions, differences in proportion of dysplastic lesions and flat dysplastic lesions. We also measured the time of each strategy. We used a fixed effects model. In cases of significant heterogeneity, we used DerSimonian–Laird random effects model.[2] We performed the data analysis using the Comprehensive Meta Analysis version 2.2 (Biostat, Englewood, NJ) statistical package.

To calculate the incremental yield or proportion of lesions detected per patient by CE, we subtracted the yield (or proportion of lesions) of WLE from that of CE. We calculated the number needed to test (NNT) using the inverse of the incremental yield. We compared the rate of dysplasia and flat dysplasia detected using CE with targeted biopsy vs WLE with targeted biopsy by calculating the odds ratio. We compared the miss rate using the odds ratio. We computed the miss rate for CE with target biopsy as any dysplasia detected by random biopsy alone; and the miss rate for WLE as any dysplasia detected by CE with targeted biopsy or by random biopsy in studies with a tandem colonoscopy design; and by random biopsy alone in the studies with randomized controlled or observational two arm designs. We measured the time of the procedure, using the pooled weighted mean difference.

We used the Cochran's Q to test heterogeneity among pooled estimates.[3] We measured statistical heterogeneity by using the I^2 statistic that quantifies the proportion of inconsistency in individual studies that cannot be explained by chance.[3] Values of I^2 equal to 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively. Finally, in order to exclude an excessive influence of any one study we evaluated whether exclusion of each study substantially affected the magnitude or statistical significance of the summary odds ratio. In order to test for publication bias we used a test for asymmetry of the funnel plot proposed by Egger et al.[4] If visual inspection of the funnel plot or the Egger's regression intercept suggested publication bias we also performed the Duval and Tweedie nonparametric trim-and-fill procedure.[5]

Results

We identified 6 unique studies involving 665 patients, of whom 72 patients had any grade of dysplasia in the analysis from 125 potentially relevant articles (Supplementary Figure 1). These 6 studies [6–11] provided data on the yield of detection of dysplasia (low or high grade) and on targeted lesion detection. Four studies [6,8–10] provided data on flat lesion detection. Four studies [6,8,9,11] provided data on time taken for procedure and 5 studies[7–11] provided data on miss rates. The characteristics of the studies included are shown in Table 1. We excluded one study[12] because the method used was targeted rather than pancolonic CE and another study because of report of dishonesty of performance of research study.[13] The quality of the studies assessed by the QUADAS tool is given in Supplementary Table 2.

The pooled incremental yield of CE over WLE for the detection of any grade of dysplasia per patient was 7% (95% CI: 3.3%–10.3%) (Figure 2 and Supplementary Table 3). CE detected dysplasia in 59 patients compared to 28 patients with WLE. The NNT to detect one extra patient with dysplasia was 14.3 (95% CI: 9.7–30.3). Note that the NNT should be interpreted with caution as it was derived from studies with variable prevalence of dysplasia.[14]

Using CE with targeted biopsy, the likelihood of detecting any dysplasia was approximately 9 times higher than using WLE––the pooled odds ratio was 8.9 (95% CI 3.4–23.0). CE detected 86 targeted lesions in these 6 studies compared to 27 detected using WLE. Using CE with targeted biopsy, the likelihood of detecting nonpolypoid dysplasia was 5 times higher than using WLE—the pooled odds ratio was 5.2 (95% CI 1.7–15.9). CE detected 45 flat lesions compared to 6 by WLE in the 4 studies, which provided data on flat lesion detection. Using CE with targeted biopsy, the likelihood to miss dysplasia was 93% lower—the pooled odds ratio was 0.07 (95% CI 0.03–0.21). Five studies reported on missed lesions. In 4 of the studies, CE did not miss any lesions; and in one, random biopsy alone discovered 2 lesions. In contrast, WLE missed a total of 58 lesions. Notably, missed lesions were defined as dysplastic lesions detected by random biopsy alone or by the alternative modality and since in studies with a tandem colonoscopy design random biopsies were done prior to CE with targeted

biopsy the definition of missed lesions for this analysis has been weighted against CE.

The pooled increase in time for CE over WLE was 10.9 minutes (95% CI 9.1–12.9 minutes). The mean procedure time ranged from 35.5 minutes to 45 minutes for CE and 22.18 to 35 minutes for WLE. All studies included in the meta-analysis took standard random (nontargeted) quadrantic biopsies every 10 cm in addition to chromoendoscopy. Thus, the procedure time may be prolonged as a result of these random biopsies.

We did not note heterogeneity ($I^2 = 0\%$) between the studies for all variables. We did not find a change in the significance of the pooled results by excluding each study in turn for any of the analysis. We ruled out publication bias by examining for funnel plot asymmetry and Eggers regression asymmetry test. For the analysis of IY on a per patient basis, where Egger's test was positive, we performed a sensitivity analysis by using the trim-and-fill method[5]. The imputed hypothetical negative unpublished studies produced a symmetrical funnel plot (Supplementary Figure 3). The pooled analysis incorporating the hypothetical studies continued to be statistically significant with a pooled IY of 5.8% (95% CI 2.8%–8.8%). We have reported the results of the sensitivity and publication bias analysis in Supplementary Table 4. (Supplementary Figures 2 & 3).

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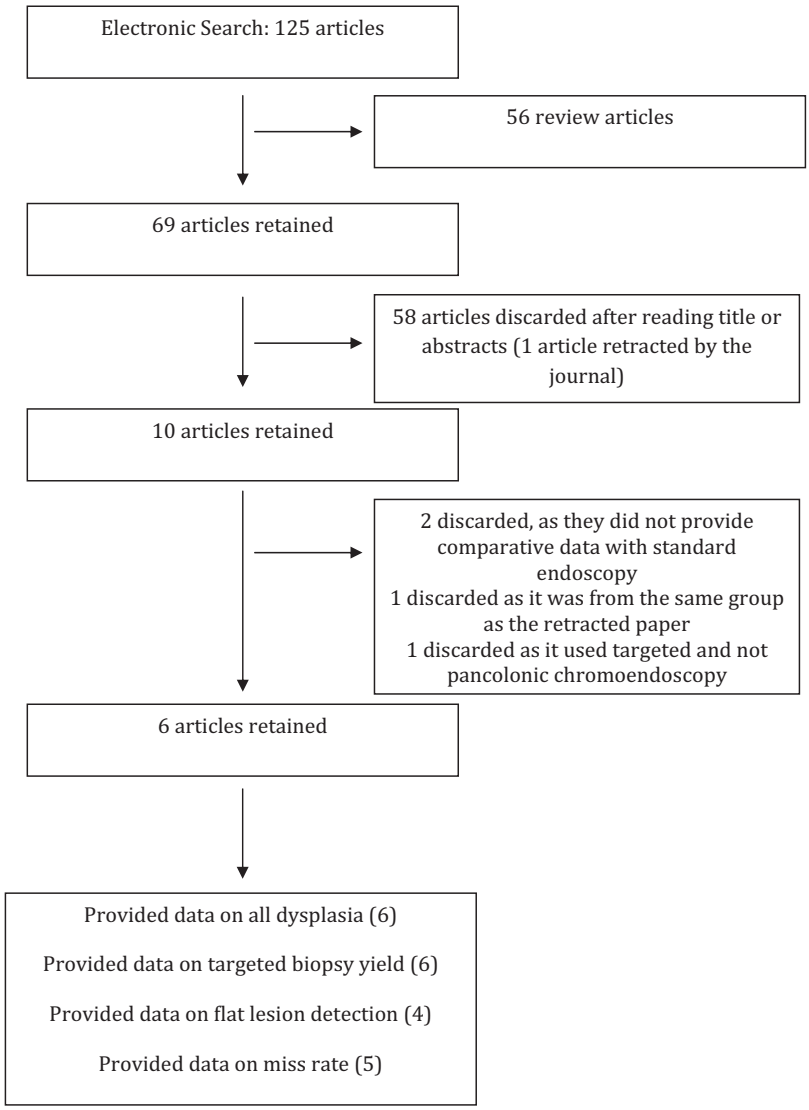
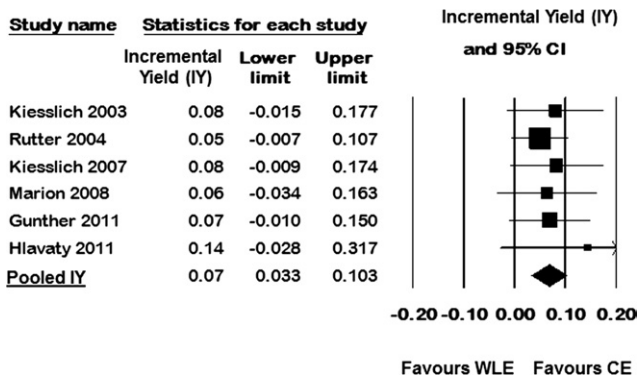
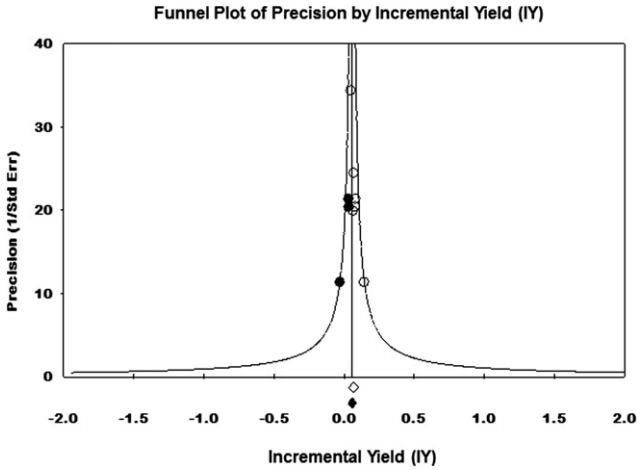


Supplementary Figure 1. Flow chart of the included articles from the electronic search.



Supplementary Figure 2. Forest plot to show incremental yield of Chromoendoscopy (CE) over standard white light endoscopy (WLE) in detection of dysplastic lesions in patients with ulcerative colitis or colonic Crohn's disease.



Supplementary Figure 3. Duval and Tweedie's trim and fill Funnel Plot to determine potential publication bias for the studies included in the incremental yield (IY) of chromoendoscopy over white light endoscopy in detection of dysplasia in patients with ulcerative colitis/colonic Crohn's disease. The x-axis (measure of effect size) represents the IY with CE versus WLE and the y-axis (measure of study precision) represents a measure of the size of the study. The centerline represents summary statistic—that is, the pooled IY of CE. The two-side hyperboles represent 95% confidence intervals. The white circles represent observed studies and the black circles are the imputed studies, the white diamond is the observed pooled IY while the black diamond is the pooled IY including the imputed studies.

Supplementary Table 1. Characteristics of the Studies Included in the Meta-analysis of the Diagnostic Yield of Dysplastic Lesions With Chromoendoscopy (CE) and Standard White Light Endoscopy (WLE) in Patients With Ulcerative Colitis

First author	Country, Year	Number of endoscopists	Dye	Type of CE	Study design	Patients included	N
Kiesslich[7]	Germany, 2003	Multiple	MB	Pancolonic	Randomized 1:1	Long standing UC ≥8 years	165
Rutter[10]	UK, 2004	Single	IC	Pancolonic	Prospective cohort, WLE followed by CE	Long standing extensive UC	100
Kiesslich[8]	Germany, 2007	Multiple	MB	Pancolonic	Randomized 1:1	Long standing UC ≥8 years	153
Marion[9]	USA, 2008	Multiple	MB	Pancolonic	Prospective cohort, WLE followed by CE	Extensive UC or Crohn's colitis involving > 1/3 of colon	102
Günther[5]	Germany, 2011	Multiple	IC	Pancolonic	Subdivided retrospectively into 50 patients in each group	Extensive UC > 8 years or colonic Crohn's > 10 years	100
Hlavaty[6]	Slovkia, 2011	Multiple	IC	Pancolonic	Retrospective analysis based on consent for WLE alone or WLE followed by CE	Pancolitis > 8 years or left sided colitis > 15 years	45

IC, indigo carmine; MB, methylene blue; UC, ulcerative colitis.

Supplementary Table 2. Application of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) Tool to the Six Studies Included in the Meta-analysis

First author	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Kiesslich 2003[7]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	N
Rutter[11]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N	N
Kiesslich 2007[8]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	N
Marion[9]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	U	U
Günther[5]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Hlavaty[6]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N

N, no; U, unclear; Y, yes.

1. Was the spectrum of patient's representative of the patients who will receive the test in practice?
2. Were selection criteria clearly described?
3. Is the reference standard likely to classify the target condition correctly?
4. Is the period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5. Did the whole sample or a random selection of the sample receive verification using a reference standard?
6. Did patients receive the same reference standard regardless of the index test result?
7. Was the reference standard independent of the index test (ie, the index test did not form part of the reference standard)?
8. Was the execution of the index test described in sufficient detail to permit replication of the test?
9. Was the execution of the reference standard described in sufficient detail to permit its replication?
10. Were the index test results interpreted without knowledge of the results of the reference standard?
11. Were the reference standard results interpreted without knowledge of the results of the index test?
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
13. Were uninterruptable/intermediate test results reported?
14. Were withdrawals from the study explained?

Supplementary Table 3. Results of the Pooled Analysis for Outcomes of Interest, Heterogeneity Analysis and the Type of Model Used for Studies Comparing Chromoendoscopy (CE) and White Light Endoscopy (WLE) for Surveillance Colonoscopy in Colonic Inflammatory Bowel Disease

Outcome	Number of studies	Number of patients	Results of pooled analysis (95% CI)	Heterogeneity analysis: Cochran's Q (*P* value)	Heterogeneity analysis: Higgins I^2	Type of model used
Number of patients with dysplasia	6	665	6% (3.1–9.8%)[a]	1.31 (0.9)	0%	Fixed effects
Dysplastic lesions detected by targeted biopsy	6	665	8.9 (4.1–20.4)[b]	3.44 (0.63)	0%	Fixed effects
Flat dysplastic lesions on targeted biopsy	4	518	5.2 (1.7–15.9)[b]	0.216 (0.9)	0%	Fixed effects
Miss rate	5	565	0.07 (0.03–0.21)[c]	2.21 (0.70)	0%	Fixed effects
Duration of procedure	4	520	10.9 (9.1–12.6)[d]	2.92 (0.41)	0%	Fixed effects

[a]Pooled incremental yield.
[b]Pooled odds ratio of CE compared to WLE.
[c]Pooled odds ratio of lesions missed (defined as dysplastic lesions detected by random biopsy alone or by the alternative modality).
[d]Pooled differences in mean time taken for procedure in minutes.

Supplementary Table 4. Results of Sensitivity Analysis and Publication Bias for Studies Comparing Chromoendoscopy and Standard White Light Endoscopy for Surveillance Colonoscopy in Colonic Inflammatory Bowel Disease

Outcome	Eggers test intercept and 95% CI	Loss of significance with exclusion of any study
Number of patients with dysplasia	1.48 (0.76–2.21)	No
Dysplastic lesions detected by targeted biopsy	0.74 (−0.67–3.40)	No
Flat dysplastic lesions on targeted biopsy	0.44 (−1.12–1.99)	No
Miss rate	0.95 (−4.61–1.44)	No
Duration of procedure	0.01 (−9.6–9.6)	No