**Surveillance in inflammatory bowel disease: is chromoendoscopy the only way to go? A systematic review and meta-analysis of randomized clinical trials**

**Authors**  
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**ABSTRACT**

**Background and study aims**  
Ulcerative colitis (UC) and Crohn’s disease (CD) have higher risk of colorectal cancer (CRC). Guidelines recommend dysplasia surveillance with dye-spraying chromoendoscopy (DCE). The aim of this systematic review and meta-analysis was to review all randomized clinical trials (RCTs) available and compare the efficacy of different endoscopic methods of surveillance for dysplasia in patients with UC and CD.

**Methods**  
Databases searched were Medline, EMBASE, Cochrane and SCIELO/LILACS. It was estimated the risk difference (RD) for dichotomous outcomes (number of patients diagnosed with one or more dysplastic lesions, total number of dysplastic lesions diagnosed and number of dysplastic lesions detected by targeted biopsies) and mean difference for continuous outcomes (procedure time).

**Results**  
This study included 17 RCTs totaling 2,457 patients. There was superiority of DCE when compared to standard-definition white light endoscopy (SD-WLE). When compared with high-definition (HD) WLE, no difference was observed in all outcomes (number of patients with dysplasia (RD 0.06; 95% CI [-0.01, 0.13])). Comparing other techniques, no difference was observed between DCE and virtual chromoendoscopy (VCE – including narrow-band imaging [NBI], i-SCAN and flexible spectral imaging color enhancement), in all outcomes except procedure time (mean difference, 6.33 min; 95% CI, 1.29, 11.33). DCE required a significantly longer procedure time compared with WLE (mean difference, 7.81 min; 95% CI, 2.76, 12.86).

**Conclusions**  
We found that dye-spraying chromoendoscopy detected more patients and dysplastic lesions than SD-WLE. Although no difference was observed between DCE and HD-WLE or narrow-band imaging, the main outcomes favored numerically dye-spraying chromoendoscopy, except procedure time. Regarding i-SCAN, FICE and auto-fluorescence imaging, there is still not enough evidence to support or not their recommendation.

**Introduction**

Inflammatory bowel disease (IBD) is a chronic, relapsing condition that affects the gastrointestinal tract, causing significant long-term morbidity. It is composed of two main entities: ulcerative colitis (UC) and Crohn’s disease (CD) [1].

Patients with UC and CD have an increased risk of colorectal cancer (CRC), which is associated with the duration, extent, and inflammatory activity of the disease [2–4]. International guidelines recommend that colonoscopic CRC surveillance be initiated 8 years after diagnosis in patients with UC pancolitis form...
or left colitis and in patients with CD and involvement of at least one third of the colon [3, 5–8].

A recent Cochrane review showed that surveillance increased the rate of detection of early CRC and consequently reduced mortality in these patients [1]. However, the best form of screening is still subject to discrepancies.

Standard definition white light endoscopy (SD-WLE) with random mucosal biopsies is historically the most widely used method, but it is time consuming, expensive, has low accuracy for diagnosis of flat lesions, and is often poorly adopted in clinical practice [9–11]. Biopsies directed to abnormal mucosa with aid of dye-spraying chromoendoscopy (DCE) are recognized as the preferred surveillance method in comparison with random biopsies and are capable of increasing detection of neoplastic lesions of the digestive tract [12–16]. The most commonly used dyes include methylene blue and indigo carmine. DCE has been shown to be superior in the detection of dysplastic lesions and is recommended by several international guidelines as the preferred endoscopic method [3, 6–8, 17].

Technological improvements in SD-WLE have been evaluated in different studies and demonstrated increased mucosal recognition and better surveillance of dysplasia [9, 18–22]. New and advanced endoscopic technologies significantly improved the resolution of the images compared to conventional white light endoscopy, as dysplasia became easier to see from the greater detail of the images [9]. Among these improvements are high definition (HD) systems, higher magnification capacities, and other image enhancement techniques, such as auto fluorescence imaging (AFI) and virtual chromoendoscopy (VCE), which includes narrow-band imaging (NBI) [23], i-SCAN, and flexible spectral imaging color enhancement (FICE). High-resolution endoscopy (1080 system) provides image signals with a higher pixel density than the conventional white light system (480 system), leading to sharper images with fewer artifacts.

With the evolution in image resolution and specialization in optical diagnosis, the advantage of DCE as a gold standard of surveillance over other methods is currently a matter of debate [9]. Considering that there is currently no evidence to support the universal adoption of one of the techniques as the most effective for detecting dysplasia in surveillance colonoscopies, a systematic review and meta-analysis of randomized clinical trials comparing two or more different surveillance techniques in this population was performed. We sought to compare the efficacy of different endoscopic techniques for diagnosis of dysplasia in patients with UC and CD.

Materials and methods

This systematic review and meta-analysis follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and was registered in the International prospective register of systematic reviews (PROSPERO) of the York University Review and Dissemination Center (CRD42018109774) [24].

Eligibility criteria

We included randomized clinical trials (RCT) available in electronic databases that compared efficacy of screening techniques for colon dysplasia in patients with UC or CD. A dysplastic lesion was defined as neoplastic epithelium without evidence of tissue invasion, characterized by low or high degree dysplasia, according to the Vienna classification [25]. Screening techniques included standard white-light colonoscopy (SD-WLE), high-definition white light colonoscopy (HD-WLE), dye chromoendoscopy (DCE), virtual chromoendoscopy (NBI, i-Scan, and FICE) and AFI. Patients presented with UC in the form of pancolitis or left colitis or DC with involvement of at least one-third or more of a segment of the colon, with a disease time of more than 8 years, or with primary sclerosing cholangitis, regardless of disease time [26–28]. There was no restriction of period, country or language of publication. We excluded studies that included screening for colon dysplasia in the general population, hereditary polyposis syndrome, and small bowel neoplasia in patients with IBD.

Search, paper selection, and data extraction

The electronic databases used to search were Medline, EMBASE, Scielo/LILACS and Cochrane/CENTRAL. Two independent authors performed the search and selection of studies [RHR and IBR]. Divergences were resolved in consensus with a third author [EGHM]. The last search occurred on January 3, 2019. The search strategy is summarized in Supplementary Fig. 1.

Evaluated outcomes

The evaluated outcomes were: number of patients diagnosed with one or more dysplastic lesions, total number of dysplastic lesions detected, number of dysplastic lesions detected by directed biopsies, and procedure time.

Risk of bias

The Cochrane Risk of Bias Tool for Randomized Controlled Trials (RoB tool) was used to assess risk of bias in the studies and consider the domains of random sequence generation, allocation concealment, selective information, blinding of participants and staff, blinding of outcomes evaluation, incomplete data and other biases. The quality of evidence was evaluated by the Grading of Recommendations Assessment, Development and Evaluation Working Group (GRADE) [29].

Synthesis measures

The risk difference (RD) and the Mantel-Haenszel test were used for dichotomous variables and the mean difference (MD) and the inverse variance for continuous variables, with a 95 % confidence interval (CI). Median and extracted intervals were transformed into mean and standard deviation by the formula of Wan et al [30].

Fixed-effect (FE) or random-effect (RE) models were adopted depending on the heterogeneity observed between the studies, determined by the inconsistency calculated by the Higgins test (I²). Inconsistency values of 25 %, 50 %, and 75 % were considered low, moderate, and high heterogeneity, respective-
ly [31]. FE models were adopted if the inconsistency was less than 50% and RE models were used equal to or greater than 50%.

Sensitivity and specificity of the techniques regarding histopathological results were extracted from the studies or calculated from values of true-positive, true-negative, false-positive, and false-negative patients.

Statistical analyzes were performed using Review Manager software (RevMan 5) Version 5.3.5 (Cochrane Collaboration, London, UK) and OpenEpi (Open SUUCe Epidemiologic Statistics for Public Health, Atlanta, United States). The relationship between study size and treatment effect for each outcome was graphically analyzed using a forest plot. Risk of publication bias analyzed using a funnel plot and Egger’s test.

Results
Selection and study characteristics
A total of 13,458 records were identified in the electronic databases (Fig. 1). Three hundred fifty-eight were removed by duality and the remaining 13,100 records were evaluated by title and abstract. A total of 13,060 records were excluded and the remaining 40 papers were evaluated for full text. In the end, 17 studies [9, 18–21, 23, 32–42] were included for meta-analysis, all of which were randomized clinical trials, which totaled 2,457 subjects. Descriptive characteristics of the studies are presented in Table 1.

Biases and evidence quality
The risks of biases in the 17 studies, according to the Cochrane RoB Tool, are completely presented in Supplementary Fig. 2. Random sequence generation was adequate in 10 studies (59%) and uncertain in seven (41%). Allocation concealment was adequate in eight studies (47%) and uncertain in nine (53%). Blinding of the team and participants was adequate in 10 studies (59%) and uncertain in seven (41%). Blinding of outcome verification was adequate in 8 studies (47%) and uncertain in 9 (53%). The presentation of incomplete outcomes was adequate in 11 studies (65%) and uncertain in six (35%). Selective data collection was adequate in 9 studies (53%) and uncertain eight studies (47%). The GRADE for quality of evidence is found in Supplementary Fig. 3.

Evaluated outcomes – comparison: DCE versus WLE
Number of patients diagnosed with one or more dysplastic lesions
There was an increase in the detection rate of patients with one or more dysplastic lesions with DCE compared to WLE (RD 0.06; 95% CI [0.03, 0.10]; NNT: 17). The rate increase was significant when the DCE was compared to the subgroup of SD-WLE (RD 0.13; 95% CI [0.04, 0.23]; NNT: 8) was observed, which did not occur when compared to HD-WLE (RD −0.00; 95% CI [−0.33, 0.33]).

After sensitivity analysis, it was detected that the high heterogeneity (I² = 82%) found in this analysis was due to the study by Iacucci et al [9], which presented a treatment effect divergent from the other included studies (Fig. 3).

Total number of dysplastic lesions detected
There was no difference in the detection rate of the number of dysplastic lesions when DCE was compared to WLE (RD 0.09; 95% CI [−0.01, 0.19]). However, in the subgroup analysis, an increase in the detection rate with DCE compared to SD-WLE (RD 0.13; 95% CI [0.04, 0.23]; NNT: 8) was observed, which did not occur when compared to HD-WLE (RD −0.00; 95% CI [−0.33, 0.33]).

Number of dysplastic lesions detected by targeted biopsies
There was no difference in the rate of dysplastic lesions detection by guided biopsies between DCE and WLE (RD 0.08; 95% CI [−0.07, 0.43]). However, in the subgroup analysis, there was an increase in the detection rate with DCE compared to SD-WLE (RD 0.33, 95% CI [0.07, 0.59], NNT: 3), which was not observed when compared to HD-WLE (RD 0.18; 95% CI [−0.07, 0.43]) (Supplementary Fig. 4). The high heterogeneity in this analysis is also due to the study by Iacucci et al [9].
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<td>210</td>
<td>305</td>
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<td>51</td>
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<td>14 (9) to 16 (9)</td>
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<td>13</td>
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<td>22 (13) to 22 (11)</td>
<td>16 (10) to 18 (8)</td>
<td>21 (10) to 21 (11)</td>
<td>15 (6) to 16 (9)</td>
<td>15 (7) to 17 (9)</td>
<td>23 (10)</td>
<td>14 (6) to 16 (7)</td>
<td>12 (9) to 14 (8)</td>
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<td>16</td>
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<td>79</td>
<td>75</td>
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<td>NA</td>
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<td>66</td>
<td>96</td>
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<td>43</td>
<td>48</td>
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Procedure time

Procedure times were measured in different ways. While the studies included in the SD-WLE subgroup considered total colonoscopy time, those in the HD-WLE subgroup considered device withdrawal time.

There was an increase in procedure time with DCE compared to WLE (MD 7.81 minutes; 95% CI [2.76, 12.86]). Subgroup analysis showed an even greater increase in procedure time with DCE compared to SD-WLE (MD 13.41 minutes; 95% CI [7.51, 19.52]). However, between DCE and HD-WLE, there was no difference in procedure time (MD 2.42 minutes, 95% CI [-2.20, 7.04]) (▶Fig. 4).

Evaluated outcomes – comparison: DCE versus VCE

Number of patients diagnosed with one or more dysplastic lesions

There was no difference in the detection rate of patients with one or more dysplastic lesions between DCE and VCE (which included NBI, i-SCAN, and FICE) (RD 0.08, 95% CI [-0.01, 0.17]). Regarding the VCE subgroups, NBI had no difference from DCE (RD 0.04, 95% CI [-0.05, 0.13]). In the other two subgroups (i-Scan and FICE) only one study was included in each. Iacucci et al [9] showed that there was no difference between DCE and i-SCAN (RD 0.09, 95% CI [-0.03, 0.21]), while Gulati et al [32] showed that DCE was superior to FICE (RD 0.26, 95% CI [0.08, 0.045, NNT 4) (▶Fig. 5).

Total number of dysplastic lesions detected

There was no difference between DCE and VCE regarding the number of dysplastic lesions detected (RD 0.10, 95% CI [-0.02, 0.21]). Regarding the VCE subgroups, NBI did not present difference from DCE (RD 0.06, 95% CI [-0.08, 0.21]). In the other two subgroups (i-Scan and FICE) Iacucci et al [9], showed no difference with i-SCAN (RD 0.04, 95% CI [-0.09, 0.18]), while Gulati et al [32] showed superiority of FICE (RD 0.30, 95% CI [0.11, 0.50, NNT 3) (▶Fig. 6).

Number of dysplastic lesions detected by targeted biopsies

There was no difference in detection rate of dysplastic lesions by directed biopsies between DCE and VCE (RD 0.00; 95% CI [-0.06, 0.06]), including subgroup analyses (DCE and NBI: RD 0.00, 95% CI [-0.08, 0.08]) (DCE and i-SCAN: RD 0.00; 95% CI [-0.08, 0.08]) (Supplementary Fig. 5).

Procedure time

There was an increase in device withdrawal time with DCE in relation to VCE (MD 6.63 minutes, 95% CI [1.29, 11.37]). In the subgroup analysis, there was an increase in withdrawal time with DCE compared to NBI (MD 9.64 minutes, 95% CI [3.26, 16.01]) and FICE (MD 4.70 minutes, 95% CI [2.01, 7.39]), but not when comparing it to i-SCAN (MD 0.90 minutes, 95% CI [-0.3, 2.10]) (▶Fig. 7).
Evaluated outcomes – comparison: WLE versus VCE

Number of patients diagnosed with one or more dysplastic lesions

There was no difference in detection rate of the number of patients diagnosed with one or more dysplastic lesions between HD-WLE and NBI (RD 0.01; 95% CI [−0.10, 0.11]) (Supplementary Fig. 6). The study by Gulati et al [32], that compared SD-WLE to FICE, did not provide data related to this outcome.

Total number of dysplastic lesions detected

There was no difference in the number of dysplastic lesions detected between WLE and VCE (RD −0.13; 95% CI [−0.39, 0.12]). Regarding the VCE subgroups, there was no difference between NBI and WLE (RD −0.02; 95% CI [−0.13, 0.08]). Cassinoti et al [35], compared FICE with SD-WLE and showed greater detection of dysplastic lesions with FICE (RD −0.39, 95% CI [−0.56, −0.21], NNT: 3) (Supplementary Fig. 7).

Number of dysplastic lesions detected by targeted biopsies

There was no difference in the detection rate of dysplastic lesions by directed biopsies between WLE and VCE (RD 0.06; 95% CI [−0.12, 0.24]). Only one study was included in each subgroup and there was no difference between HD-WLE and NBI (RD 0.17, 95% CI [−0.18, 0.51]) and between SD-WLE and FICE (RD 0.00, 95% CI [−0.16, 0.16]) (Supplementary Fig. 8).

Procedure time

There was a reduction in device withdrawal time with HD-WLE compared to NBI (MD −1.55 minutes; 95% CI [−2.75, −0.36]). The study comparing SD-WLE and FICE did not provide procedure time data (Supplementary Fig. 9).

Evaluated outcomes – comparison: AFI and other techniques

Number of patients diagnosed with one or more dysplastic lesions

There was no difference in the detection rate of patients with one or more dysplastic lesions between the AFI and the group of other techniques (RD 0.03; 95% CI [−0.19, 0.25]). There was no difference in the study that compared AFI and DCE (RD −0.07, 95% CI [−0.16, 0.03]) and in the study that compared AFI and HD-WLE (RD 0.16; 95% CI [−0.04, 0.36]) (Supplementary Fig. 10).
Total number of dysplastic lesions detected

There was no difference in the number of dysplastic lesions detected between AFI and other techniques (RD 0.02; 95 % CI [–0.48, 0.51]). Both studies included presented divergent results. There were fewer lesions detected by AFI compared to DCE (RD –0.23, 95 % CI [–0.34, –0.12; NNT 4]) and an increase in the number of lesions detected by AFI compared to HD-WLE (RD 0.28; 95 % CI [0.05, 0.51]) (Supplementary Fig. 11).

Number of dysplastic lesions detected by targeted biopsies

There was no difference in the detection of dysplastic lesions by directed biopsies between the AFI and the group of other techniques (RD –0.13; 95 % CI [–0.30, 0.04]) (Supplementary Fig. 12).

Procedure time

There was no difference in device withdrawal time with AFI compared to other techniques (MD –3.40 minutes, 95 % CI [–10.56, 3.76]). There was a reduction in procedure time in the study by Vieuvels et al [18], that compared AFI to DCE (MD –7.11 minutes; 95 % CI [–9.68, –4.54]) but not in the study by van den Broek et al [19], that compared AFI to HD-WLE (MD 0.20 minutes; 95 % CI [–1.66, 2.06]) (Supplementary Fig. 13).

Sensitivity and Specificity

Sensitivity and specificity regarding histopathological results are presented in Supplementary Table 1.

Sensitivity of SD-WLE ranged from 50 % to 80 %. HD-WLE showed sensitivity between 91 % and 100 % and specificity of 78 %. DCE sensitivity varied between 63 % and 100 % and specificity between 79 % and 98 %. NBI showed sensitivity between 50 % and 83 %. i-SCAN showed sensitivity of 91 % and specificity of 62 % and FICE sensitivity from 95 % to 100 % and specificity from 78 % to 96 %. AFI sensitivity ranged from 83 % to 87 % and specificity was 97 %.

Discussion

We identified 17 RCTs with 2457 patients, comparing the performance of seven different colonoscopy dysplasia surveillance techniques in patients with inflammatory bowel disease: HD-WLE, DCE, VCE (including NBI, FICE and i-SCAN), and AFI.

In the majority of evaluated outcomes, there was high heterogeneity (I² > 50 %) between included studies. Random effect models were adopted for more conservative analyses. The consequence of this was the disappearance of subtle differences.
between techniques that, in the fixed-model analysis, could exist due to the treatment effect of larger studies.

DCE detected a greater number of patients with dysplasia, greater number of dysplastic lesions, and greater number of dysplastic lesions detected by directed biopsies when compared to WLE. The differences obtained with DCE, however, were significant only regarding the subgroup of SD-WLE. Three studies compared DCE versus HD-WLE, 22 % (54/242) of patients were noted to have dysplasia using DCE compared with 16 % (41/251) using HD-WLE (RD 6 %; 95 % CI [–0.3% to 13%]). Despite non-significance almost every analysis favored numerically DCE in the main outcomes versus HD-WLE.

The absence of difference between HD-WLE and DCE is due to the influence of the treatment effect of Iaccuci et al [9] on the meta-analysis. The study presented HD-WLE with equal results in outcomes, diverging from the results of Mohammed et al [20] and Park et al [21], who also compared DCE with HD-WLE showing DCE superiority.

The other two VCE subgroups, i-Scan and FICE, presented only with one study each [9, 32]. Due to the limited number of studies, it is not yet possible to determine whether there is a difference between techniques.

In addition, the comparison between NBI and HD-WLE showed no difference in the number of patients and number of dysplastic lesions detected. As NBI also uses high-definition image during virtual chromoscopic evaluation, the result suggests that the benefit observed in comparison with HD-WLE may be more associated with high definition imaging.

When detection between two techniques is similar, time can be a key factor. DCE, despite provoking an increase of 13.41 minutes compared to SD-WLE, is still preferable by detecting more patients and lesions. However, compared to HD-WLE or NBI, DCE requires the same or longer procedure time respectively (9.63 minutes longer than NBI). The additional procedure time and consequently, sedation time, could increase adverse effects but it can also increase dysplasia detection due to a more thorough exam.

AFI did not allow for subgroup analysis as it presented with only two studies comparing it with different techniques, DCE and HD-WLE. In both studies, AFI presented discordant performance. While in Vleugels et al [18] AFI was lower than DCE for detection of total dysplastic lesions, in Van Den Broek et al [19] AFI was superior to HD-WLE. Regarding the number of patients with dysplasia, there was no significant difference in AFI.
with the compared technique. According to the results, it is still not possible to recommend or not as a surveillance method to the detriment of DCE and HD-WLE, given the low quality of the current evidence.

The current guidelines [3, 17, 43, 44] recommend that DCE with directed biopsies be the method of choice for neoplastic surveillance in patients with IBD. Guidelines have pointed out the low-quality evidence in specific in relation to the high-definition era and that one cannot extrapolate the benefit of DCE necessarily from the prior standard definition eras. Three recently published systematic reviews with network meta-analysis compared the efficacy of different endoscopic techniques for dysplasia surveillance in people with IBD.

Bessissow et al [45] included 8 randomized controlled trials. This meta-analysis compared only 4 techniques (DCE, NBI, HD-WLE and SD-WLE) and they did not identify any single technique superior to all in dysplasia detection. They also included in their analysis data from one crossover trial that did not provide the results for the first phase of the study. In our analysis we added nine more randomized trials, hence comparing seven techniques. We concluded that DCE was superior to SD-WLE and there was a trend in favoring DCE over other techniques.

Imperatore et al [46] included 27 studies, but most of them were low-quality, such as prospective non-randomized and observational studies. They identified only a significant superiority of DCE over WLE in detecting dysplasia, while no other single technique was found to be superior to all others in dysplasia detection. The authors combined SD and HD-WLE in the same arm in comparison to other techniques and was not made sub-analysis even though these techniques require distinct endoscopes and have different image resolution.

Iannone et al [47] concluded that full spectrum high definition white-light endoscopy (FUSE) may represent the first-line approach for dysplasia surveillance. However, this conclusion is not supported by the evidence.}

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DCE</th>
<th>VCE</th>
<th>Risk difference</th>
<th>Risk difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, random, 95% CI</td>
</tr>
<tr>
<td>2.1.1 DCE vs NBI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feitosa 2011</td>
<td>4</td>
<td>13</td>
<td>8.5%</td>
<td>0.31 [0.05, 0.57]</td>
</tr>
<tr>
<td>Pelisse 2011</td>
<td>4</td>
<td>27</td>
<td>13.9%</td>
<td>0.03 [-0.15, 0.20]</td>
</tr>
<tr>
<td>Bisshops 2017</td>
<td>14</td>
<td>74</td>
<td>19.6%</td>
<td>0.02 [-0.10, 0.14]</td>
</tr>
<tr>
<td>Watanabe 2016</td>
<td>14</td>
<td>130</td>
<td>25.0%</td>
<td>- 0.01 [-0.09, 0.06]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>244</td>
<td>265</td>
<td>66.9%</td>
<td>0.04 [-0.05, 0.13]</td>
</tr>
<tr>
<td>Total events</td>
<td>36</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 5.50, df = 3 (P = 0.14); I² = 45%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.81 (P = 0.42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 2.1.2 DCE vs i-Scan |        |       |        |                  |                  |
| Iacucci 2018       | 22     | 90    | 20.1%  | 0.09 [-0.03, 0.21] |
| Subtotal (95% CI)  | 90     | 90    | 20.1%  | 0.09 [-0.03, 0.21] |
| Total events       | 22     | 14    |        |                  |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 1.50 (P = 0.13) |

| 2.1.3 DCE vs FICE  |        |       |        |                  |                  |
| Gulati 2018        | 6      | 23    | 13.0%  | 0.26 [0.08, 0.45] |
| Subtotal (95% CI)  | 23     | 25    | 13.0%  | 0.26 [0.08, 0.45] |
| Total events       | 6      | 0     |        |                  |
| Heterogeneity: Not applicable |
| Test for overall effect: Z = 2.76 (P = 0.006) |

Total (95% CI) | 357 | 380 | 100.0% | 0.08 [-0.01, 0.17] |
| Total events   | 64   | 48   |        |                  |
| Heterogeneity: Tau² = 0.01; Chi² = 12.12, df = 5 (P = 0.03); I² = 59% |
| Test for overall effect: Z = 1.84 (P = 0.07) |
| Test for subgroup differences: Chi² = 4.42, df = 2 (P = 0.11), I² = 54.7% |

- Fig. 5 DCE versus VCE: number of patients diagnosed with one or more dysplastic lesions.
In surveillance of IBD, HD-WLE and NBI, for the obtained results, are shown to be promising for dysplasia surveillance in patients with IBD. More studies are necessary to demonstrate if these techniques can supplant DCE as the method of choice.

Limitations

There are intrinsic limitations to any meta-analysis in combining results from different clinical trials. Six studies included in this study are abstracts, which makes it impossible to interpret risks of bias. Four other trials used the crossover format in the study design. In this case, the accuracy of the techniques used cannot be compared directly. In addition, to avoid the carry-over effect, the results were extracted only from the first evaluation of these studies.

Another important limitation is the lack of information regarding the appropriate training of the endoscopists to perform the DCE, VCE, and AFI. Less training and consequently less expertise in a given technique can impair performance and impact effectiveness of the method. One potential downside of encouraging surveillance by one methodology over another is concern that physicians for instance experienced in WLE/NBI need not feel compelled to perform DCE if not experienced. Guidelines have emphasized the need for proper training when making surveillance methodology decision making including the AGA 2010 [48] and ESGE 2014 [17].

Furthermore, it was not possible to perform separate analysis on the efficacy of dysplasia screening techniques in the different patient populations with inflammatory bowel disease (Crohn’s disease and ulcerative colitis) because the selected studies included mixed populations and no separate analysis of the two diseases.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DCE Events</th>
<th>VCE Events</th>
<th>Risk difference M-H, random, 95% CI</th>
<th>Risk difference M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Total</td>
<td>M-H, random</td>
<td></td>
</tr>
<tr>
<td><strong>2.2.1 DCE vs NBI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisshop 2017</td>
<td>31</td>
<td>21</td>
<td>17.9 %</td>
<td>0.17 [0.02, 0.31]</td>
</tr>
<tr>
<td>Feitosa 2011</td>
<td>3</td>
<td>13</td>
<td>12.0 %</td>
<td>0.23 [-0.01, 0.47]</td>
</tr>
<tr>
<td>Pelissé 2011</td>
<td>5</td>
<td>27</td>
<td>14.2 %</td>
<td>-0.03 [-0.23, 0.18]</td>
</tr>
<tr>
<td>Watanabe 2016</td>
<td>16</td>
<td>130</td>
<td>22.1 %</td>
<td>-0.05 [-0.14, 0.04]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>244</td>
<td>265</td>
<td>66.2 %</td>
<td>0.06 [-0.08, 0.21]</td>
</tr>
<tr>
<td>Total events</td>
<td>55</td>
<td>51</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2.2.2 DCE vs i-Scan</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iacucci 2018</td>
<td>27</td>
<td>90</td>
<td>19.0 %</td>
<td>0.04 [-0.09, 0.18]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>90</td>
<td>90</td>
<td>19.0 %</td>
<td>0.04 [-0.09, 0.18]</td>
</tr>
<tr>
<td>Total events</td>
<td>27</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2.2.3 DCE vs FICE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gulati 2018</td>
<td>7</td>
<td>23</td>
<td>14.8 %</td>
<td>0.30 [0.11, 0.50]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>23</td>
<td>25</td>
<td>14.8 %</td>
<td>0.30 [0.11, 0.50]</td>
</tr>
<tr>
<td>Total events</td>
<td>7</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>357</td>
<td>380</td>
<td>100.0 %</td>
<td>0.10 [-0.02, 0.21]</td>
</tr>
<tr>
<td>Total events</td>
<td>89</td>
<td>74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.01; Chi² = 9.77, df = 3 (P = 0.02); I² = 69 %
Test for overall effect: Z = 0.89 (P = 0.37)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.51)

Heterogeneity: Not applicable
Test for overall effect: Z = 3.09 (P = 0.002)

Heterogeneity: Tau² = 0.01; Chi² = 17.11, df = 5 (P = 0.004); I² = 71 %
Test for overall effect: Z = 1.63 (P = 0.10)
Test for subgroup differences: Chi² = 5.25, df = 2 (P = 0.07), I² = 61.9 %

![Fig. 6] DCE versus VCE: total number of dysplastic lesions detected.
As important as the detection rate of dysplasia would be the extraction of CRC-related mortality data and time to interval cancer, which is the focal point of surveillance in patients with IBD. A randomized clinical trial is unlikely to assess these outcomes given the need for prolonged follow-up, which can be better assessed by observational studies.

**Conclusion**

We found that DCE detected more patients and dysplastic lesions than standard-definition white-light endoscopy. Although no difference was observed between DCE and HD-WLE or NBI, the main outcomes favored numerically dye-spraying chromoendoscopy, except procedure time. Regarding i-SCAN, FICE and auto-fluorescence imaging, there is still not enough evidence to support or not their recommendation.

**Acknowledgements**

The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine Hospital das Clínicas.

**Competing interests**

Dr. Hourneaux de Moura is a consultant for Boston Scientific and Olympus.

**References**


[21] Park SJ, Kim HS, Yang DH et al. High definition chromoendoscopy with water-jet versus high definition white light endoscopy in the detection of dysplasia in long standing ulcerative colitis: a multicenter prospective randomized controlled study. Gastroenterology 2016; 150: S1270

[22] de Rocha RSP, Ribeiro IB, de Moura DTH et al. Sodium picosulphate or polyethylene glycol before elective colonoscopy in outpatients: A systematic review and meta-analysis World J Gastrointest Endosc 2018; 10: 422–441


[26] Soetikno RM, Lin OS, Heidenreich PA et al. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: A meta-analysis. Gastrointest Endosc 2002; 56: 48–54

[27] Flores BM, O’Connor A, Moss AC. Impact of mucosal inflammation on risk of colorectal neoplasia in patients with ulcerative colitis: a systematic review and meta-analysis. Gastrointest Endosc 2017; 86: 1006–1011.e8


[33] Alexandersson B, Hamad Y, Andreasson A et al. Su1689 comparison of chromoendoscopy versus white light endoscopy in surveillance of chronic colitis – a randomized single center study including random biopsies. Gastrointest Endosc 2018; 87: AB370

[34] Watanabe K, Nishishita M, Shimamoto F et al. 722 Comparison between newly-developed narrow band imaging and panchroendoendoscopy for surveillance colonoscopy in patients with longstanding ulcerative colitis: a prospective multicenter randomized controlled trial, navigator study. Gastrointest Endosc 2016; 83: AB172


Farraye FA, Odze RD, Eaden J et al. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. Gastroenterology 2010; 138: 738–745