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

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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-definiton 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 (I^2). 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 SoUCe 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 duplicity 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**.

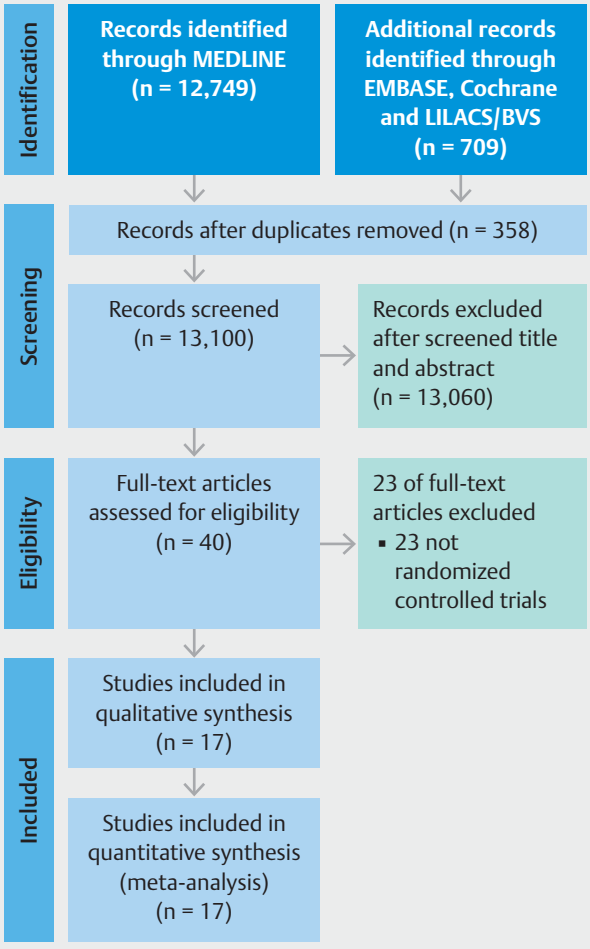
Biases and evidence quality

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 0.06, 95 % CI [0.03, 0.10], NNT: 17) and was not observed when compared to the HD-WLE subgroup (RD 0.06; 95 % CI [–0.01, 0.13]) (▶ **Fig. 2**).



▶ **Fig. 1** Flow diagram of the study.

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]).

After sensitivity analysis, it was detected that the high heterogeneity ($I^2 = 82$ %) 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**).

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 0.18; 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].

▶ **Table 1** Characteristics of the included studies.

Study	Gulati [32]	Iacucci [9]	Bis-schops [23]	Vleu-gels [18]	Alexan-dersson [33]	Park [21]	Wata-nabe [34]	Cassi-noti [35]	Moham-med [20]	Freire [36]	Ignjato-vic [37]	Feitosa [38]	Pellisé [39]	Van den Broek [42]	Van den Broek [19]	Kies-slich [41]	Kies-slich [40]
Year	2018	2018	2018	2018	2018	2016	2016	2015	2015	2014	2012	2011	2011	2011	2008	2007	2003
Type and design of study	Article, Parallel	Article, Parallel	Article, Parallel	Article, Parallel	Ab-stract, Parallel	Ab-stract, Parallel	Ab-stract, Parallel	Ab-stract, Parallel	Ab-stract, Parallel	Article, Parallel	Article, Parallel	Ab-stract, Parallel	Article, Cross-over	Article, Cross-over	Article, Cross-over	Article, Parallel	Article, Parallel
Endo-scopic tech-nique com-paration	DCE, FICE	DCE, HD-WLE, i-SCAN	DCE, NBI	DCE, AFI	DCE, SD-WLE	DCE, HD-WLE	DCE, NBI	SD-WLE, FICE	DCE, HD-WLE	DCE, SD-WLE	HD-WLE, NBI	DCE, NBI	DCE, NBI	HD-WLE, NBI	AFI, HD-WLE	DCE, SD-WLE	DCE, SDWLE
Type of dye	Indigo carmine	Indigo carmine	Methy-lene Blue	Indigo carmine and Me-thylene Blue	Indigo carmine	Indigo carmine	Indigo carmine	NA	Indigo carmine	Methy-lene Blue	NA	NA	Indigo carmine	NA	NA	Methy-lene Blue	Methy-lene Blue
Patients, n	60	270	157	210	305	210	263	91	103	162	112	29	60	48	50	153	174
Type of IBD (pa-tients, n)	UC (45), CD (03),	UC (129), CD (136), IC (5)	UC (157)	UC (210)	UC (NA), CD (NA)	UC (210)	UC (263)	UC (91)	UC (103)	UC (162)	UC (112)	UC (13), CD (16)	UC (42), CD (19)	UC (48)	UC (50)	UC (161)	UC (174)
Mean age (SD), y	41 (12) to 48 (15)	48 (14) to 50 (12)	52 (14) to 52.5 (13)	56 (12)	50	NA	51	NA	54 (14) to 56 (16)	49 (13) to 52 (16)	52 (11) to 53 (14)	49 to 50	47 (13) to 49 (15)	56 (11)	50 (11) to 51 (13)	42 (20) to 46 (23)	39 (9) to 42 (12)
Sex M/F	30/18	148/122	73/58	122/88	210/95	NA	136/127	NA		74/88	65/47	10/19	33/27	35/13	31/19	NA	
Duration of IBD (SD), y	12 (5) to 17 (7)	16 (10) to 19 (10)	14 (9) to 16 (9)	19 (10) to 22 (13)	NA	NA	13	NA	22 (13) to 22 (11)	16 (10) to 18 (8)	21 (10) to 21 (11)	15 (6) to 16 (9)	15 (7) to 17 (9)	23 (10)	14 (6) to 16 (7)	12 (9) to 14 (8)	10 (6) to 11 (7)
Left-sided (UC)	NA	49	54	68	NA	NA	NA	NA	0	79	16	NA	NA	0	0	53	54
Pancoli-tis (UC)	36	79	75	142	NA	NA	NA	NA	103	66	96	NA	43	48	50	38	83
History of dys-plasia, n	5	60	NA	34	NA	NA	15	NA	NA	0	9	NA	8	9	7	NA	0

▲ **Table 1** (Continuation)

Study	Gulati [32]	Iacucci [9]	Bisschops [23]	Vleugels [18]	Alexandersson [33]	Park [21]	Watanabe [34]	Cassinoti [35]	Mohammed [20]	Freire [36]	Ignjatovic [37]	Feitosa [38]	Pellisé [39]	Van den Broek [42]	Van den Broek [19]	Kiesslich [41]	Kiesslich [40]
Family history of CCR, n	2	29	NA	34	NA	NA	7	NA	6	23	14	NA	8	7	NA	NA	8
Personal history of PSC, n	24	35	13	38	NA	NA	2	NA	19	0	4	NA	5	8	7	15	19

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

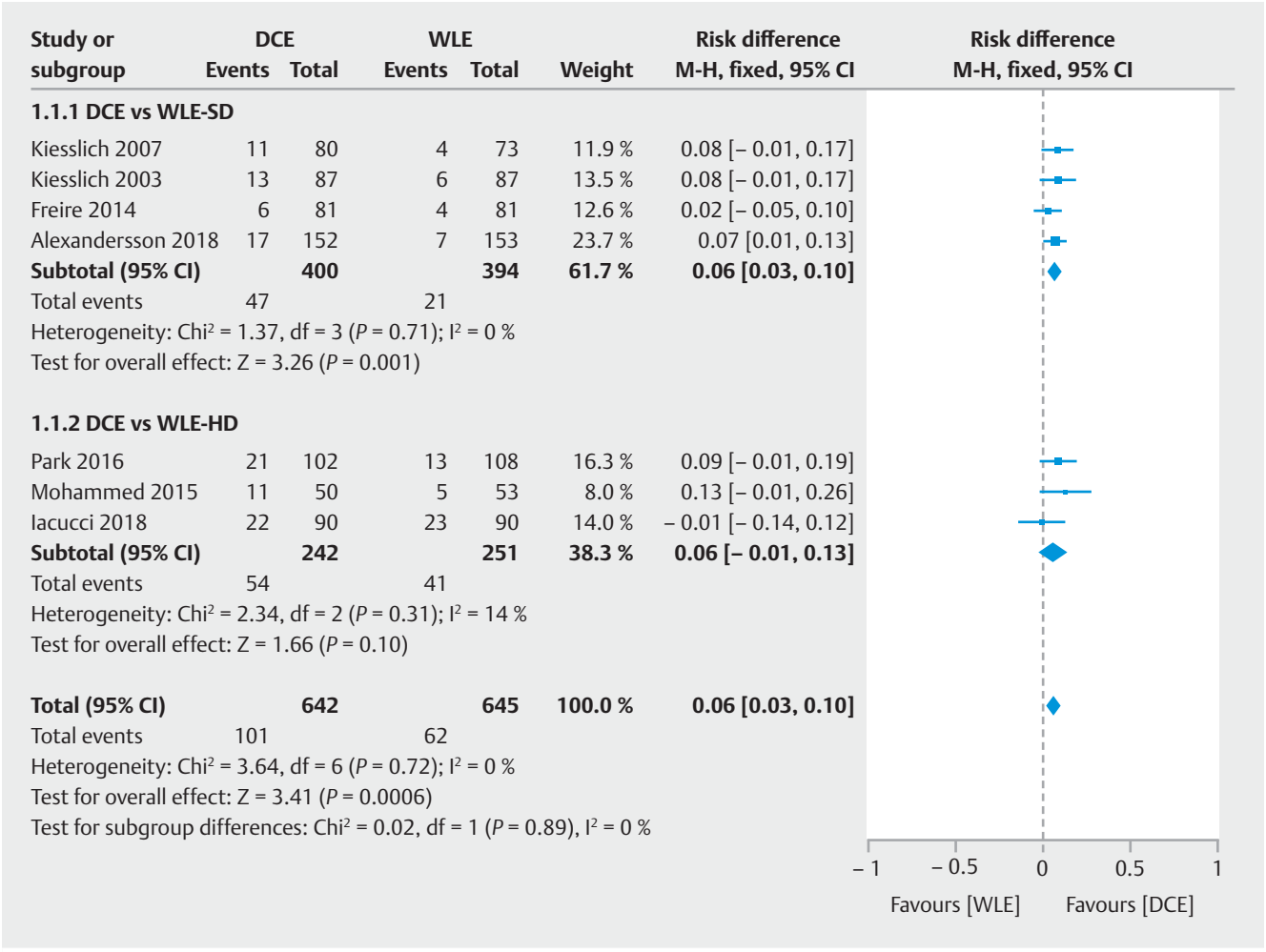
There was no difference between DCE and VCE regarding the number of dysplastic lesions detected (RD 0.10, 95 % CI [–0.02, 0.21]). Regarding the VCE subgroups, NBI did not present difference from DCE (RD 0.06, 95 % CI [–0.08, 0.21]). In the other two subgroups (i-Scan and FICE) Iacucci et al [9]. showed 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 [6.88, 12.41]) and FICE (MD 5.70 minutes, 95 % CI [2.39, 9.01]), but not when comparing it to i-SCAN (MD 0.90 minutes, 95 % CI [–0.3, 2.10]) (▶ **Fig. 7**).



▶ **Fig. 2** DCE versus WLE: number of patients diagnosed with one or more dysplastic lesions.

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**).

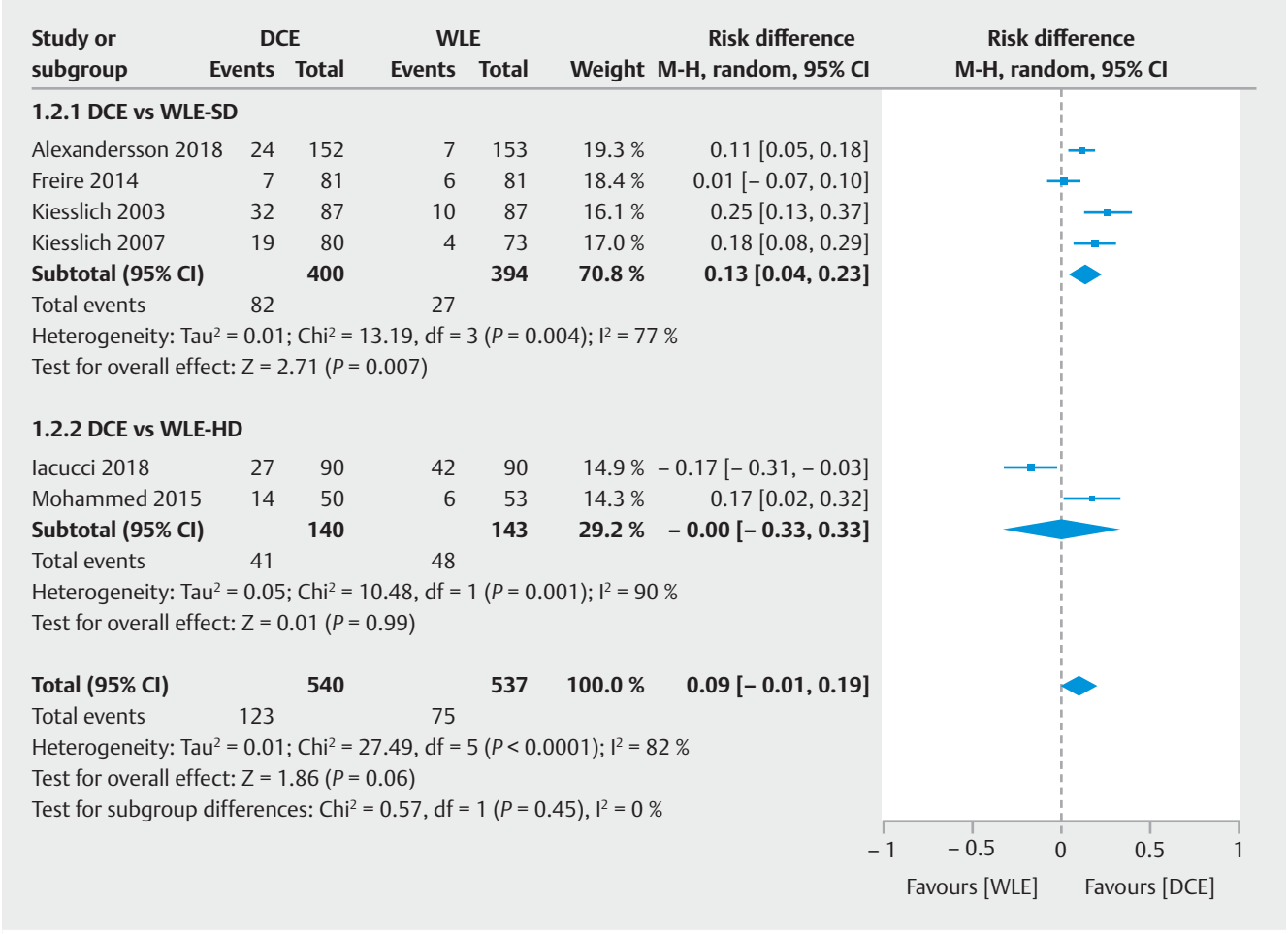
Procedure time

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**).



▶ **Fig. 3** DCE versus WLE: total number of dysplastic lesions detected.

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 Vieugels 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**.

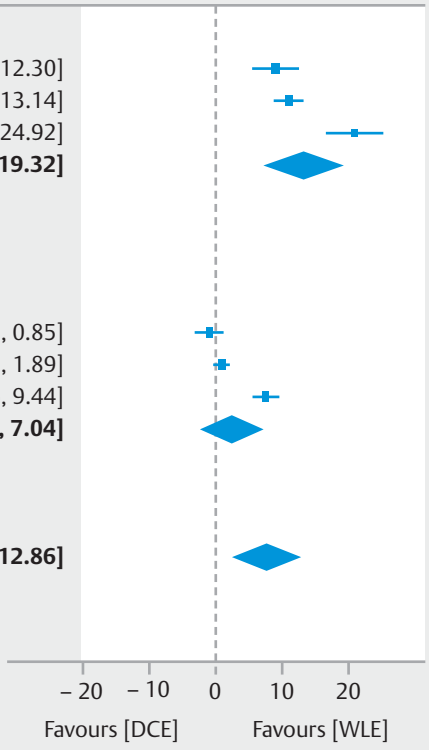
Sensitivity of SD-WLE ranged from 50 % to 80 %. HD-WLE showed sensitivity between 91 % and 100 % and specificity of 78 %. DCE sensitivity varied between 63 % and 100 % and specificity between 79 % and 98 %. NBI showed sensitivity between 50 % and 83 %. i-SCAN showed sensitivity of 91 % and specificity 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 ($I^2 > 50\%$) between included studies. Random effect models were adopted for more conservative analyses. The consequence of this was the disappearance of subtle differences

Study or subgroup	DCE Mean	DCE SD	DCE Total	WLE Mean	WLE SD	WLE Total	Weight	Mean difference IV, random, 95% CI
1.9.1 DCE vs WLE-SD								
Kiesslich 2003 (1)	44	12.2	84	35	9.3	81	16.2 %	9.00 [5.70, 12.30]
Kiesslich 2007 (2)	42	7.23	80	31	6.28	73	16.9 %	11.00 [8.86, 13.14]
Freire 2014 (3)	61.5	15.6	72	40.7	8.7	73	15.6 %	20.80 [16.68, 24.92]
Subtotal (95% CI)			**236**			**227**	**48.7 %**	**13.41 [7.51, 19.32]**
Heterogeneity: Tau² = 24.51; Chi² = 21.53, df = 2 (*P* < 0.0001); I² = 91 %								
Test for overall effect: Z = 4.45 (*P* < 0.00001)								
1.9.2 DCE vs WLE-HD								
Park 2016 (4)	17.8	7.3	102	18.9	7.1	108	17.0 %	– 1.10 [– 3.05, 0.85]
Iacucci 2018 (5)	16.2	4.67	90	15.4	2.43	90	17.3 %	0.80 [– 0.29, 1.89]
Mohammed 2015 (6)	21.2	5.8	50	13.6	3.3	53	17.0 %	7.60 [5.76, 9.44]
Subtotal (95% CI)			**242**			**251**	**51.3 %**	**2.42 [– 2.20, 7.04]**
Heterogeneity: Tau² = 15.94; Chi² = 50.02, df = 2 (*P* < 0.00001); I² = 96 %								
Test for overall effect: Z = 1.03 (*P* = 0.30)								
Total (95% CI)			**478**			**478**	**100.0 %**	**7.81 [2.76, 12.86]**
Heterogeneity: Tau² = 38.17; Chi² = 188.06, df = 5 (*P* < 0.00001); I² = 97 %								
Test for overall effect: Z = 3.03 (*P* = 0.002)								
Test for subgroup differences: Chi² = 8.25, df = 1 (*P* = 0.004), I² = 87.9 %								



▶ **Fig. 4** DCE versus WLE: procedure time.

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 [–1 % 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.

VCE when compared to DCE, allowed for the extrapolation of the results only for the NBI subgroup. Four studies were included in this subgroup, 15 % (36/244) of patients were noted to have dysplasia using DCE compared with 13 % (34/265) using NBI (RD 2 %; 95 % CI [–5 % to 13 %]). Despite non-significance, analysis favored numerically DCE in the main outcomes versus NBI.

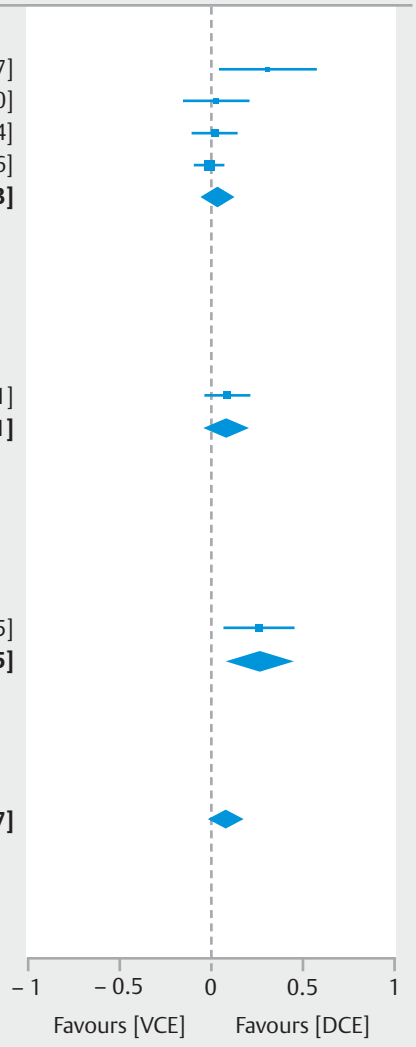
The other two VCE subgroups, i-Scan and FICE, presented with only one study each [9, 32]. Due to the limited number of studies, it is not yet possible to determine whether there is a difference between techniques.

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

Study or subgroup	DCE Events	DCE Total	VCE Events	VCE Total	Weight	Risk difference M-H, random, 95% CI
2.1.1 DCE vs NBI						
Feitosa 2011	4	13	0	16	8.5 %	0.31 [0.05, 0.57]
Pelissé 2011	4	27	4	33	13.9 %	0.03 [– 0.15, 0.20]
Bisshops 2017	14	74	14	83	19.6 %	0.02 [– 0.10, 0.14]
Watanabe 2016	14	130	16	133	25.0 %	– 0.01 [– 0.09, 0.06]
Subtotal (95% CI)		**244**		**265**	**66.9 %**	**0.04 [– 0.05, 0.13]**
Total events	36		34			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.50$, df = 3 ($P = 0.14$); $I^2 = 45$ %						
Test for overall effect: Z = 0.81 ($P = 0.42$)						
2.1.2 DCE vs i-Scan						
Iacucci 2018	22	90	14	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	0	25	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: $Tau^2 = 0.01$; $Chi^2 = 12.12$, df = 5 ($P = 0.03$); $I^2 = 59$ %						
Test for overall effect: Z = 1.84 ($P = 0.07$)						
Test for subgroup differences: $Chi^2 = 4.42$, df = 2 ($P = 0.11$), $I^2 = 54.7$ %						



▶ **Fig. 5** DCE versus VCE: number of patients diagnosed with one or more dysplastic lesions.

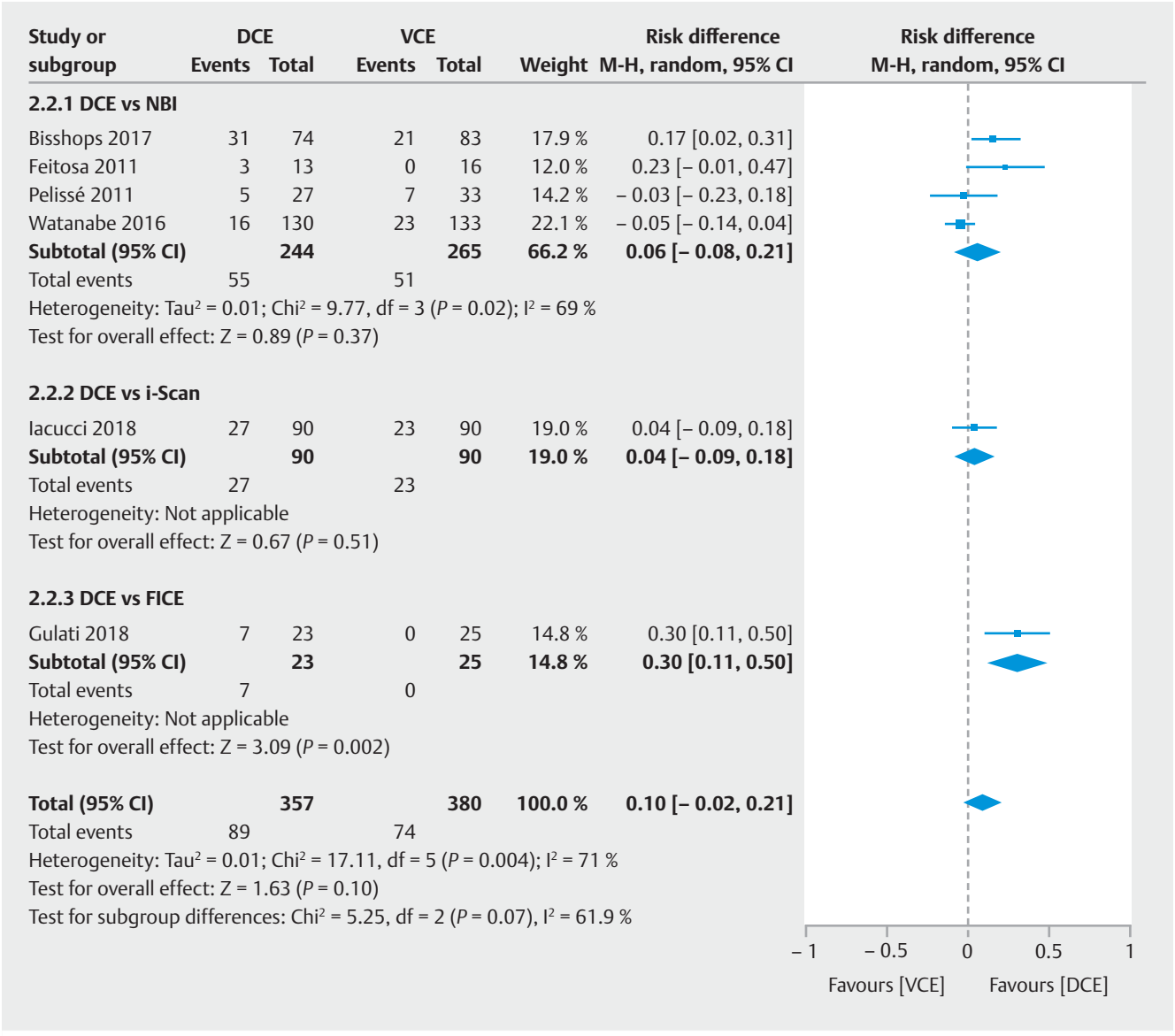
with the compared technique. According to the results, it is still not possible to recommend or not as a surveillance method to the detriment of DCE and HD-WLE, given the low quality of the current evidence.

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 can not 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



▶ **Fig. 6** DCE versus VCE: total number of dysplastic lesions detected.

based on only one crossover trial that included 55 patients that compares FUSE versus HD-WLE.

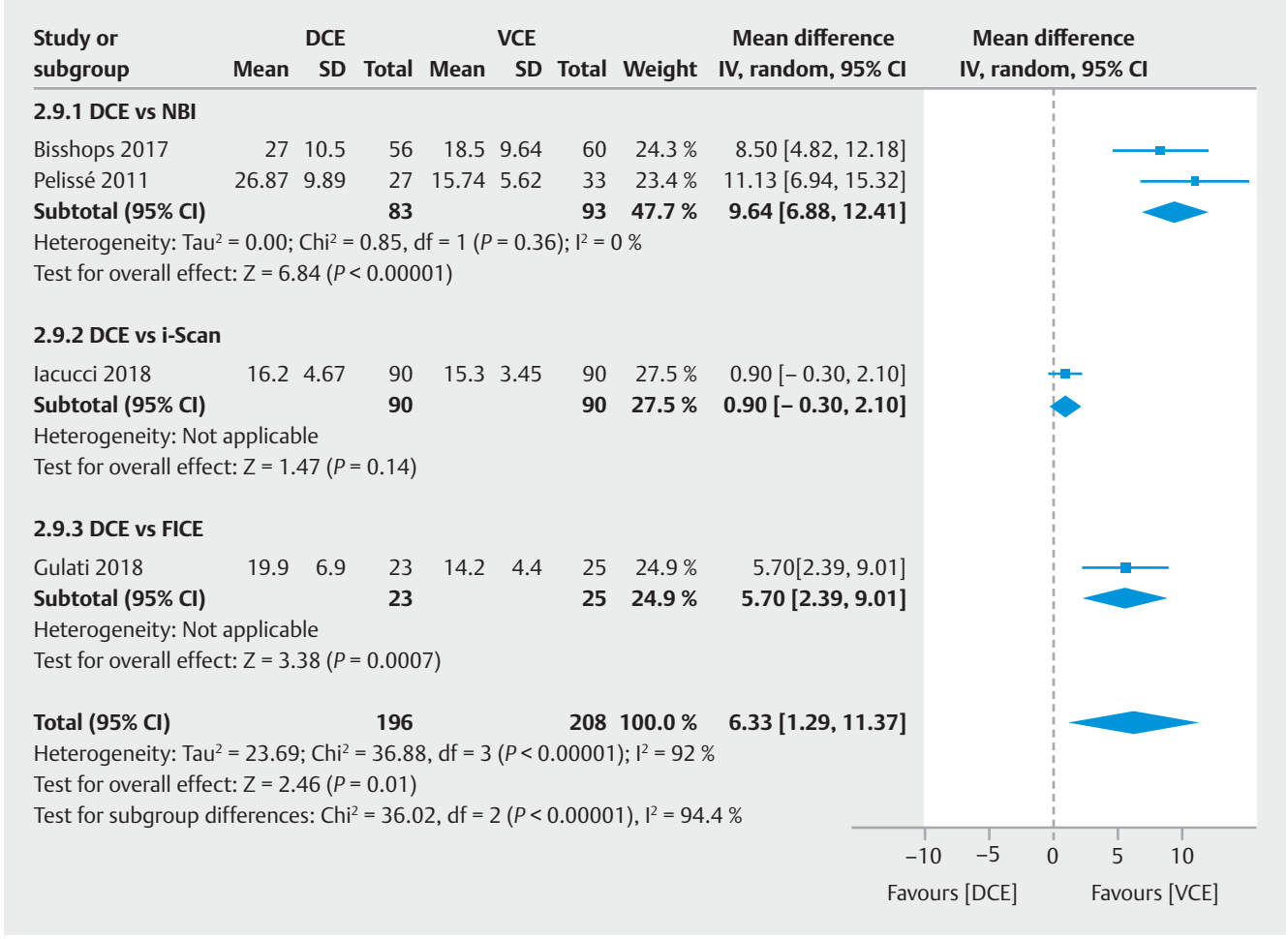
In surveillance of IBD, HD-WLE and NBI, for the obtained results, are shown to be promising for dysplasia surveillance in patients with IBD. More studies are necessary to demonstrate if these techniques can supplant DCE as the method of choice.

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.



▶ **Fig. 7** DCE versus VCE: procedure time.

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.

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Competing interests

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

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