Comparative Efficacy and Safety of Endoscopic Modalities for Colorectal Cancer Screening in Inflammatory Bowel Disease: A Systematic Review and Network Meta-analysis

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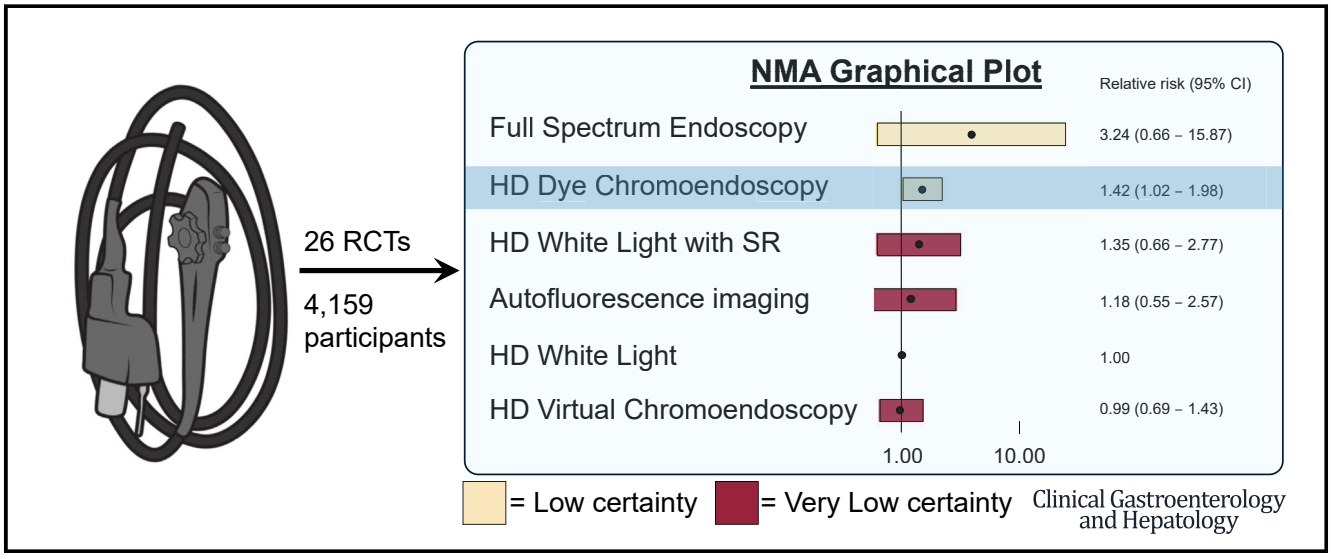

BACKGROUND & AIMS: **Long-standing inflammatory bowel disease (IBD) increases the risk of colonic neoplasia, necessitating effective screening strategies. This network meta-analysis compared the efficacy and safety between different endoscopic modalities in the high-definition (HD) era.**

*Authors share co-first authorship.

Abbreviations used in this paper: AFI, autofluorescence imaging; BSG, British Society of Gastroenterology; CADe, computer-aided detection; CD, Crohn's disease; CE, chromoendoscopy; CI, confidence interval; CRC, colorectal cancer; CRN, colorectal neoplasia; DCE, dye-based chromoendoscopy; FUSE, full-spectrum endoscopy; GDG, guideline development group; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HD, high definition; IBD, inflammatory bowel disease; MD, mean difference; NBI, narrow band imaging; NMA, network meta-analyses; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses; RCT, randomized controlled trial; RoB, risk of bias; RR, risk ratio; SD, standard definition; SOP, Standard Operating Procedure; SR, segmental reinspection; SUCRA, surface under the cumulative ranking curve; UC, ulcerative colitis; VCE, virtual chromoendoscopy; WLE, white-light endoscopy.

1542-3565
https://doi.org/10.1016/j.cgh.2024.11.008

METHODS: We searched CENTRAL, ClinicalTrials.gov, Embase, MEDLINE, and WHO for randomized controlled trials (RCTs) comparing endoscopic modalities for screening colonoscopy in patients with IBD up to February 2024. The primary outcome was detection of any dysplastic lesion per patient. The certainty of the evidence was GRADE-assessed.

RESULTS: A total of 26 RCTs involving 4159 participants were included, comparing 6 endoscopic modalities: HD white light endoscopy (HD-WLE), HD virtual chromoendoscopy (HD-VCE), HD dye-based chromoendoscopy (HD-DCE), HD-WLE with segmental re-inspection (SR), autofluorescence imaging (AFI), and full-spectrum endoscopy (FUSE). HD-DCE may have a small benefit in detecting dysplasia over HD-WLE (low certainty, small magnitude;: relative risk [RR], 1.42; 95% confidence interval [CI], 1.02–1.98). FUSE may be no different to HD-WLE (low certainty: RR, 3.24; 95% CI, 0.66–15.87). The other modalities were assessed as very low certainty (HD-WLE with SR: RR, 1.35; 95% CI, 0.66–2.77; AFI: RR, 1.18; 95% CI, 0.55–2.57; HD-VCE: RR, 0.99; 95% CI, 0.69–1.43). Sensitivity analyses supported these findings. Limited data on serious adverse events precluded meta-analysis; 2 serious events were reported among 2164 patients (very low certainty).

CONCLUSIONS: HD-DCE is the only modality for IBD surveillance with evidence (low-certainty) demonstrating potential to detect more dysplastic lesions compared with HD-WLE. There was no evidence to support any of the other modalities as an alternative due to very low-certainty evidence.

Keywords: Chromoendoscopy; Colorectal Cancer Screening; Dye-based Chromoendoscopy (DCE); Dysplasia; Endoscopic Surveillance; High-definition Endoscopy; Inflammatory Bowel Disease (IBD); Network Meta-analysis; Virtual Chromoendoscopy (VCE); White Light Endoscopy (WLE).

Individuals with longstanding inflammatory bowel disease (IBD), including colonic Crohn's disease (CD) and ulcerative colitis (UC), face a significantly higher risk of developing colorectal cancer (CRC) due to chronic inflammation and other risk factors such as age at diagnosis, extent of colonic involvement, family history, primary sclerosing cholangitis and a previous history of dysplasia.[1–4] Despite reductions in IBD-related CRC incidence due to advanced anti-inflammatory therapies and better endoscopic surveillance, these patients still have elevated CRC risk compared with the general population.

The annual incidence rates of CRC range from 19.5 to 344.9 per 100,000 for CD and from 54.5 to 543.5 per 100,000 for UC.[5] Recent large-scale Scandinavian population-based cohort studies show that individuals with UC and CD have a 1.66-fold (95% confidence interval [CI], 1.57–1.76) and 1.40-fold (95% CI, 1.27–1.53) increased risk of CRC, respectively, compared with the general population.[1,2] These estimates, which are lower than previously reported, have remained relatively stable in recent years, likely due to advancements in disease management and surveillance strategies. The risk of CRC escalates with the duration of IBD, contributing to 10% to 15% of all-cause mortality among these patients.[6] Effective surveillance is important as it may reduce the incidence of CRC or the rate of CRC-related mortality by detecting early-stage CRC, and enhancing survival rates among patients with IBD.[7]

Given the critical need for early lesion detection in patients with IBD to manage the "inflammation-dysplasia-carcinoma sequence," research has focused on identifying the best modality for endoscopic surveillance.[3,8] The evolution from standard-definition (SD) to high-definition (HD) endoscopy, along with advancements in dye-based and virtual chromoendoscopy, has enhanced our ability to visualize and target biopsies towards areas of concern. HD endoscopy and chromoendoscopy (CE) are currently considered superior to standard white-light endoscopy (WLE) for detecting dysplasia.[9,10] A wide range of endoscopic modalities are available for CRC screening, including SD and HD WLE. Dye-based chromoendoscopy (DCE) can be performed using either SD or HD scopes to enhance mucosal visualization with dyes. Virtual chromoendoscopy (VCE) technologies such as Narrow Band Imaging (NBI) from Olympus, i-SCAN from Pentax, and FICE from Fujinon enhance visualisation without topical dye application. Additionally, autofluorescence imaging (AFI) utilises tissue autofluorescence to highlight abnormalities, and full-spectrum endoscopy (FUSE) offers an expanded field of view to improve lesion detection.[8] Recently segmental reinspection with HD white light has been proposed to enhance dysplasia detection in IBD.[11]

Efforts to clarify the optimal endoscopic technique for CRC surveillance in patients with IBD have led to numerous observational studies and randomized controlled trials (RCTs), followed by systematic reviews with meta-analysis and, more recently, network meta-analyses (NMA).[12–15] The move towards the use of meta-analysis has been driven by low frequency of dysplasia outcomes, meaning many studies were underpowered, especially for inter-modality comparisons. Challenges in previous systematic reviews and NMAs include the inclusion of a broad range of endoscopic technologies with varying resolutions and capabilities, such as SD and HD WLE, DCE, and VCE and AFI, sometimes combining both imaging techniques and/or RCTs and observational studies to increase statistical

power.[12,14,15] This diversity complicates direct and indirect comparisons of their effectiveness. Specifically, including studies that utilized SD DCE could impact the overall assessment of CE's performance, especially when compared with VCE in the era of HD scopes.[15] Additionally, the use of crossover study data may introduce carry-over effects, potentially skewing the results.[14]

Previous guidelines have supported the use of both DCE and VCE as equivalent; however, their additional benefit in the era of HD white light remains unclear.[16–18] The current NMA, part of the British Society of Gastroenterology's (BSG) initiative to update IBD surveillance guidelines, aims to address these limitations through a comprehensive identification of relevant outcomes and a risk-thresholding exercise for each outcome to aid in grading the effect size. This systematic review and meta-analysis aims to estimate the comparative efficacy and safety of these modalities and assess the certainty of the evidence using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology, aiming to provide clear guidance on the most effective endoscopic modalities for CRC surveillance in IBD, thereby enhancing patient care and outcomes.

What You Need to Know

Background

Inflammatory bowel disease increases colorectal cancer risk, necessitating effective endoscopic surveillance. Various high-definition (HD) endoscopic modalities are used, but their comparative efficacy in dysplasia detection remains unclear.

Findings

HD dye-based chromoendoscopy may improve dysplasia detection compared with other modalities like HD white light endoscopy, although evidence certainty is low. No significant differences in safety outcomes were identified.

Implications for patient care

HD dye-based chromoendoscopy may be preferred for inflammatory bowel disease surveillance due to its potential for better dysplasia detection, but further high-quality studies are needed to confirm its clinical superiority and safety.

Methods

This systematic review was conducted as part of an update to the BSG guidelines for CRC surveillance in patients with IBD. The protocol was registered on University of Central Lancashire (UCLan) online repository (https://clok.uclan.ac.uk/53182/). More complete information and data for methods and results are included in the supplementary online appendices (Supplementary Tables 1–10 and Supplementary Figures 1–4). Critical and important outcomes and magnitude effect thresholds for the judgement of imprecision (Supplementary Table 8) were predetermined at the beginning of the guidelines process, prior to the literature search, by the guideline development group (GDG).[19,20]

The detailed methodology follows the BSG's guideline development process and is available in the Standard Operating Procedure (SOP).[19,20]

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were used to design and conduct this systematic review.[21]

Literature Search and Study Selection

MEDLINE, Embase CENTRAL, ClinicalTrials.gov, and WHO ICTPR, were searched in February 2024 (See the Supplementary Appendix for search strategies and results developed by a Cochrane information specialist).

The inclusion criteria were RCTs comparing any modality for the detection of CRC in patients with IBD exclusively, from inception to current date reported as a full paper or in abstract form. Gray literature was eligible for inclusion, and no exclusions were made for IBD subtype or concurrent conditions, type of surveillance, language, participant age, or any other reasons. Crossover trials were included but only data from the pre-crossover stages were eligible. The included studies reference list of a previous systematic review on the topic was searched manually for eligible studies.[15] The GDG was asked to provide any studies they thought should be included and were not captured in the database search.

Online literature search and study selection were performed independently in duplicate at both title/abstract, and full-text screening, and disagreements were resolved by a senior reviewer, on the Covidence systematic review management software.[22]

Data Extraction and Risk of Bias Assessment

Data extraction was performed using piloted extraction forms for demographic and baseline characteristics, intervention details, and outcome data at study end. Risk of bias (RoB) assessment was assessed using the Cochrane risk of bias 1.[23] Data extraction and RoB assessment was performed independently in duplicate, and disagreements were resolved by a senior reviewer. Authors were contacted for missing or unclear outcome data and RoB clarifications (Table 1).

Outcomes

The GDG pre-determined the primary and secondary outcomes as follows:

Primary outcome:

- **Patients with at least 1 dysplastic lesion detected**: Defined as Vienna Classification 2 to 5 (indefinite for

Table 1. Patient and Included Study Demographics

Study No.	Study ID	Modality 1	Modality 2	Modality 3 (if applicable)	Abstract/ full paper	Crossover	Population	Country	Single/ multicenter	Disease severity (inactive/ mixed/ not reported)	Trial registration	Number of Endoscopists	Numbers randomized in each group (1/2/3)	Author contacted (response)
1	Kiesslich 2003[24]	Dye chromoendoscopy	White light endoscopy	N/A	Full paper	No	UC + PSC	Germany	Single	Not reported	Not reported	Not reported	84/81	Corresponding author contacted in February 2024 but no response was received
2	Kiesslich 2007[25]	Dye chromoendoscopy	White light	N/A	Full paper	No	UC + PSC	Germany	Single	Not reported	Not reported	Not reported	81/80	Not deemed necessary
3	Dekker 2007[26]	White light endoscopy	Virtual chromoendoscopy (first gen)	N/A	Full paper	Yes	UC	Netherlands	Single	Inactive	Not reported	Multiple	22/20	Author provided data and clarifications in February 2024
4	Van de Broek 2008[27]	HD white light	Auto fluorescence imaging	N/A	Full paper	Yes	UC + PSC	Netherlands	Single	Inactive	ISRCTN05272746	Multiple	25/25	Corresponding author contacted in February 2024 but no response was received
5	Van de Broek 2011[28]	HD White Light	HD Virtual Chromoendoscopy	N/A	Full Paper	Yes	UC+ PSC	Netherlands	Single	Inactive	ISRCTN56671833	Multiple	25/23	Not necessary
6	Feitosa 2011[29]	HD dye chromoendoscopy	HD virtual chromoendoscopy	N/A	Abstract/ thesis	No	UC + CD	Portugal	Single	Not reported	Not reported	Multiple	18/16	Corresponding author contacted in February 2024 but no response was received
7	Ignjatovic 2012[30]	HD white light	HD virtual chromoendoscopy	N/A	Full paper	No	UC + PSC	United Kingdom	Multicenter	Mixed	NCT00292175	Multiple	56/56	Author provided data and clarifications in February 2024
8	Drastich 2013[31]	White light endoscopy	Auto fluorescence imaging	N/A	Abstract	Yes	UC+ PSC	Czech Republic	Single	Not reported	Not reported	Not reported	NR/NR	Corresponding author contacted in February 2024 but no response was received

Table 1. Continued

Study No.	Study ID	Modality 1	Modality 2	Modality 3 (if applicable)	Abstract/ full paper	Crossover	Population	Country	Single/ multicenter	Disease severity (inactive/ mixed/ not reported)	Trial registration	Number of Endoscopists	Numbers randomized in each group (1/2/3)	Author contacted (response)
9	Freire 2014[32]	Dye chromoendoscopy	White light endoscopy	N/A	Full paper	No	UC	Portugal	Multicentre	Inactive	Not reported	Multiple	72/73	Corresponding author contacted in February 2024 but no response was received
10	Leifield 2015[33]	White light endoscopy	Narrow band imaging	N/A	Full paper	Yes	UC + PSC	Europe	Multicenter	Inactive	Not reported	Multiple	NR/NR	Not deemed necessary
11	Mohammed 2015[34]	HD dye chromoendoscopy	HD white light	N/A	Abstract/ thesis	No	UC + PSC	United Kingdom	Single	Mixed	NCT02138318	Multiple	79/79	Author provided data and clarifications in February 2024
12	Watanabe 2016 B[35]	HD dye chromoendoscopy	HD virtual chromoendoscopy	N/A	Abstract	No	UC	Japan	Multicenter	Inactive	UMIN000013527	Multiple	130/133	Corresponding author contacted in February 2024, but no response was received
14	Pelise 2017[36]	HD dye chromoendoscopy	HD virtual chromoendoscopy	N/A	Full paper	Yes	UC + CD + PSC	Spain	Single	Inactive	Not reported	Multiple	27/33	Corresponding author contacted in February 2024 but no response was received
15	Leong 2017 A[37]	HD white light	Full spectrum endoscopy	N/A	Full paper	Yes	UC + CD	Australia	Single	Inactive	ACTRN12616000047493	Multiple	27/25	Not deemed necessary
13	Iacucci 2018[38]	HD white light	HD dye chromoendoscopy	HD virtual chromoendoscopy	Full paper	No	UC + CD + PSC	Canada	Single	Inactive	NCT02098798	Single	90/90/90	Not deemed necessary
16	Gulatti 2018[39]	HD dye chromoendoscopy	HD virtual chromoendoscopy	N/A	Full paper	Yes	UC + CD + PSC	United Kingdom	Single	Inactive	NCT02543021	Multiple	25/23	Author provided data and clarifications in February 2024
17	Vleugels 2018[40]	HD dye chromoendoscopy	Auto fluorescence imaging	N/A	Full paper	No	UC + PSC	Netherlands + United Kingdom	Multicenter	Inactive	Not reported	Multiple	105/105	Author provided data and clarifications in February 2024
18	Bisschops 2018[41]	HD dye chromoendoscopy	HD virtual chromoendoscopy	N/A	Full paper	No	UC + PSC	Belgium + Canada	Multicenter	Inactive	NCT01882205	Multiple	74/83	Not deemed necessary

Table 1. Continued

Study No.	Study ID	Modality 1	Modality 2	Modality 3 (if applicable)	Abstract/ full paper	Crossover	Population	Country	Single/ multicenter	Disease severity (inactive/ mixed/ not reported)	Trial registration	Number of Endoscopists	Numbers randomized in each group (1/2/3)	Author contacted (response)
19	Lord 2018[42]	HD dye chromoendoscopy (high concentration)	HD dye chromoendoscopy (low concentration)	N/A	Abstract with thesis	No	UC + CD + IC + PSC	United Kingdom	Single	Not reported	NCT03250780	Multiple	150/150	Author provided data and clarifications in February 2024
20	Yang 2019[43]	HD white light	HD dye chromoendoscopy	N/A	Full paper	No	UC + PSC	South Korea	Multicenter	Mixed	KCT0001195: 4-2013-0622	Multiple	108/102	Corresponding author contacted in February 2024 but no response was received
21	Alexandersson 2020[44]	HD white light	HD dye chromoendoscopy	N/A	Full paper	No	UC + CD + IC + PSC	Sweden	Single	Not reported	NCT01505842	Multiple	153/152	Not deemed necessary
22	Feuerstein 2020[45]	HD white light	HD dye chromoendoscopy	N/A	Abstract	No	UC + CD + IC + PSC	United States of America	Single	Not reported	Not reported	Multiple	48/41	Corresponding author contacted in February 2024 but no response was received
23	Kandiah 2021[46]	HD white light	HD virtual chromoendoscopy	N/A	Full paper	No	UC + CD + PSC	United Kingdom	Multicenter	Inactive	Not reported	Multiple	102/102	Not deemed necessary
24	Gonzalez-Bernardo 2021[47]	HD dye chromoendoscopy	HD virtual chromoendoscopy	N/A	Full paper	No	UC + CD + PSC	Spain	Single	Inactive	Not reported	Single	67/62	Author provided data and clarifications in February 2024
25	Sinonquel 2022[48]	HD dye chromoendoscopy	HD virtual chromoendoscopy	N/A	Abstract	No	Not reported	Europe	Multicenter	Not reported	Not reported	Multiple	71/65	Corresponding author contacted in February 2024 but no response was received
26	Te Groen 2024[11]	HD white light	HD dye chromoendoscopy	HD white light with SR	Abstract	No	UC + CD + IC + PSC	Netherlands	Multicenter	Inactive	Not reported	Multiple	133/268/265	Corresponding author provided data clarification in March 2024

CD, Crohn's disease; HD, high definition; IC, indeterminate colitis; PSC, primary sclerosing cholangitis; UC, ulcerative colitis.

dysplasia, low-grade dysplasia, high-grade dysplasia, or invasive neoplasia).[49]

Secondary outcomes:

- **Patients with at least 1 dysplastic lesion detected from targeted biopsies**: Yield of dysplastic lesions (Vienna 2–5) from targeted biopsies during colonoscopy.
- **Patients with at least 1 dysplastic lesion detected from random biopsies**: Yield of dysplastic lesions (Vienna 2–5) from random biopsies, if taken.
- **Patients with at least 1 lesion of any type detected**: Includes both neoplastic (dysplastic + serrated) and non-neoplastic lesions (Vienna Classification 1–5).[49]
- **Patients with serious adverse events**: Defined as events requiring hospitalization, causing permanent disability, or being life-threatening.
- **Patients with any adverse events**: Includes all adverse events, serious or nonserious.
- **Patient withdrawals due to adverse events**: Refers to those who withdrew from the procedure due to adverse events.
- **Withdrawal times**: Time taken for withdrawal during colonoscopy. This was an additional outcome examined that was not part of the risk-thresholding exercise by the GDG.

For all primary and secondary outcomes, only lesions from biopsies taken from colitic regions were considered, excluding noncolitic areas.

Subgroup and Sensitivity Analyses

A subgroup analysis for modality subtypes (high or low concentration HD DCE, and HD VCE subtypes) and sensitivity analyses for studies including participants with inactive disease only, studies where serrated lesions were not considered, and studies with more than one endoscopists who performed the trial endoscopies, were predetermined. They were only performed for the primary outcome.

Statistical Analysis

Dichotomous outcomes were expressed in risk ratios (RRs) with corresponding 95% CIs. Continuous outcomes were expressed as mean difference (MD) with 95% CIs. The unit of analysis was the participant for all outcomes. The modified intention-to-treat method was used for analysis. The random effect model was used to pool data.

NMA methodology was used as described by Higgins et al within a frequentist framework using multivariate meta-analysis.[50] We assessed the assumption of transitivity by comparing the distribution of potential effect modifiers across the pairwise comparisons. Heterogeneity was assessed statistically using the the I^2 statistic for each pairwise comparison and with the loop-specific approach for the direct and indirect estimates. Surface under the cumulative ranking curve (SUCRA) was used to rank treatments.

Funnel plots were used to assess publication bias for pairwise analyses where there were at least 10 studies. Indirectness was assessed for outcomes.

Statistical analyses were performed using the netmeta package on R statistical software version 4.3.1. HD-WLE was used as the reference modality to which other modalities were compared for the presentation of these results. This choice aligns with current international guidelines, which emphasize that HD-WLE should be used as the baseline technique for detecting dysplasia in patients with IBD undergoing surveillance colonoscopies.[10,16]

GRADE Assessment for the Certainty of the Evidence

The GRADE framework was used to assess the certainty of the evidence. The direct and indirect evidence certainty was assessed based on risk of bias, inconsistency, indirectness, and publication bias. Following that the network evidence certainty was assessed based on imprecision and incoherence, and the contribution of the direct and indirect evidence. Two review authors (MG, VS) independently rated the certainty ratings, and disagreements were resolved by discussion and consensus. The evidence was rated as 'high,' 'moderate,' 'low,' or 'very low,' according to the GRADE framework. These findings were presented in 'GRADE Of Relative effect Diagram Of Network meta-analysis' (GORDON) plots.[51]

Results

Twenty-six RCTs were included (Figure 1).[11,24–48] The following modalities were identified: WLE with HD or SD scope, HD-WLE with segmental reinspection (SR), DCE with HD or SD scope, VCE with sub-types of NBI, FICE, and i-SCAN, as well as FUSE and AFI. The examinations with reported modalities were performed for the entire colon.

Included study characteristics, intervention details, study sponsor details, excluded studies and reasons for exclusion, ongoing and studies awaiting classification can be found in Table 1 and the Supplementary Material (Supplementary Tables 1–5).

The summary of the RoB assessment for the included studies and the detailed judgements are presented in Figure 2 and the Supplementary Material (Supplementary Table 6).

Summary of findings tables for all GRADEd outcomes with direct, indirect, and network GRADE decisions and reasons can also be found in Figures 3 and 4, Table 2, and the Supplementary Material (Supplementary Table 7).

Details on extracted outcome data and additional characteristics of the included studies are also reported

in the Supplementary Material (Supplementary Tables 9–10).

Patients With at Least One Dysplastic Lesion Detected

Twenty-three of the included studies reported this outcome.[11,24,25,27–30,32,34–48] Nineteen of them could be connected for the main NMA, comparing a total of 6 modalities (Figure 2).[11,43,44,46–48] Three studies (Freire 2014, Kiesslich 2003, and Kiesslich 2007) could not be connected to the network because they were comparing SD DCE and WLE, which were not compared in any of the other studies.[24,25,32] Lord 2018 could not be included in the main analysis because it compared high- and low-concentration HD DCE modalities; however it could be connected in subgroup analysis for modality subtypes.[42]

The overall detection rate for HD WLE was 113 per 1000 people screened.

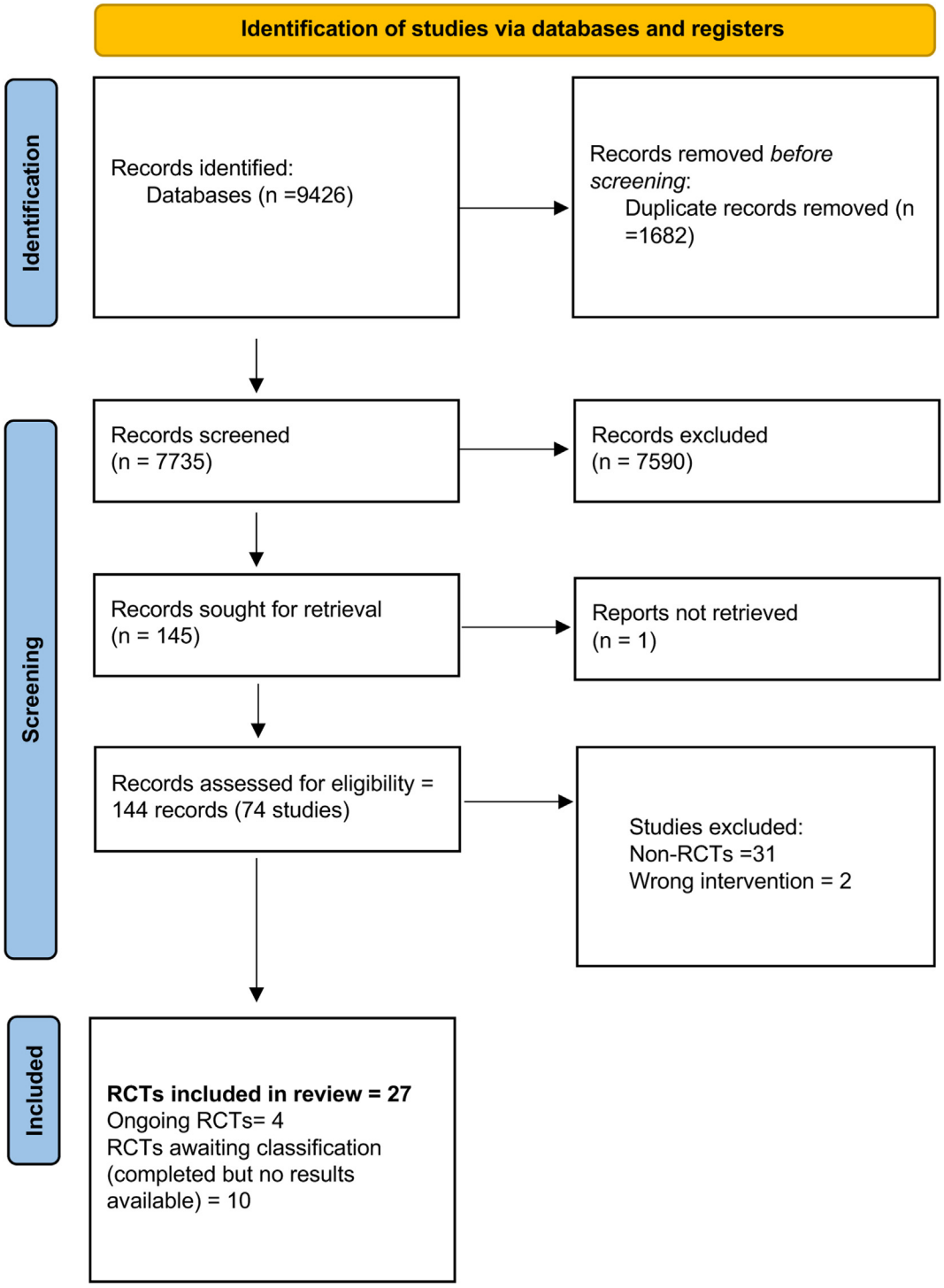

Figure 1. PRISMA diagram.

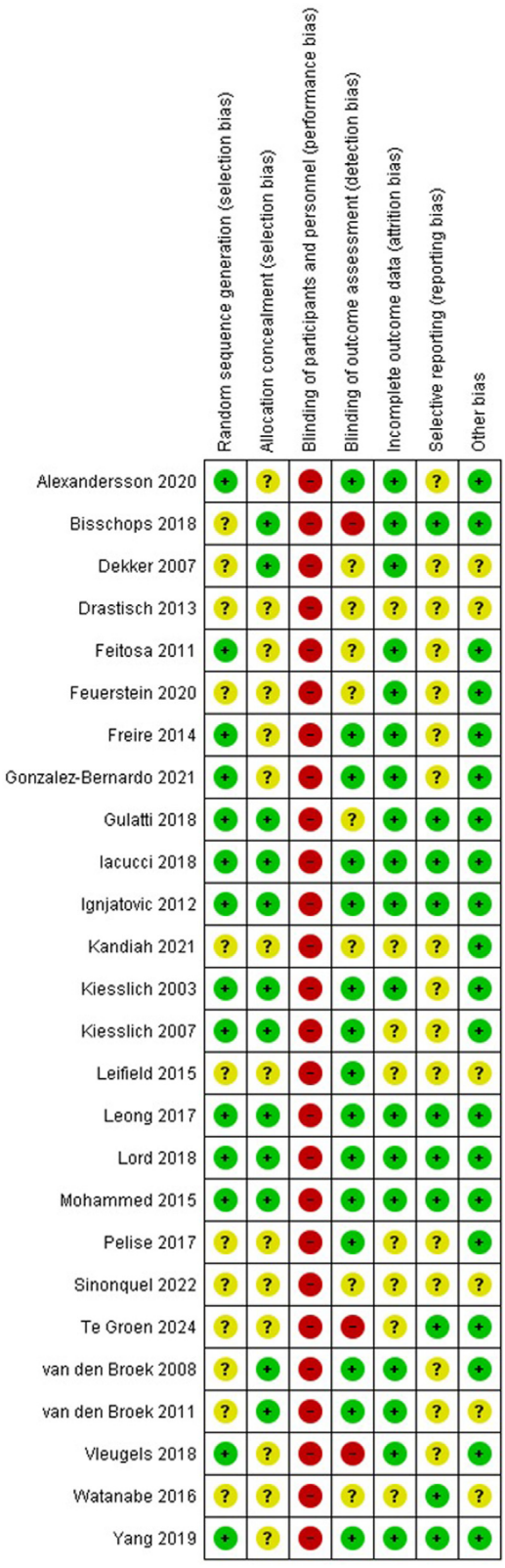

Figure 2. RoB of included studies.

No modality had high or moderate GRADE certainty ratings for this outcome.

HD DCE may be better at detecting at least one dysplastic lesion per patient compared with HD WLE (RR, 1.42; 95% CI, 1.02–1.98, small magnitude more [ranging from trivial to moderate] low GRADE certainty). FUSE may be no different to HD WLE (RR, 3.24; 95% CI, 0.66–15.87, low GRADE certainty) (Table 2 and Figure 3).

The results for HD WLE with SR (RR, 1.35; 95% CI, 0.66–2.77), AFI (RR, 1.18; 95% CI, 0.55–2.57), and HD VCE (RR, 0.99; 95% CI, 0.69–1.43) were all very low GRADE certainty, and no conclusions can be drawn.

Subgroup and sensitivity analyses. Visual inspection of the subgroup analysis for 7 modality subtypes compared with HD WLE did not reveal major deviations from the main analysis; however, the imprecision for all comparisons was high (AFI: RR, 1.17; 95% CI, 0.51–2.66; FICE: RR, 0.19; 95% CI, 0.02–1.56; FUSE: RR, 3.24; 95% CI, 0.65–16.11; HD CE high concentration: RR, 1.38; 95% CI, 0.9–2.11; HD CE low concentration: RR, 1.21; 95% CI, 0.75–1.94); I-scan: RR, 0.94; 95% CI, 0.59–1.52; NBI: RR, 1.05; 95% CI, 0.57–1.93) (Supplementary Figure 1).

We were led to similar conclusions by the sensitivity analyses for studies including participants with inactive disease only (based on specific criteria reported in each study: AFI: RR, 1.03; 95% CI, 0.49–2.15; FUSE: RR, 3.24; 95% CI, 0.7–15.07; HD DCE: RR, 1.25; 95% CI, 0.82–1.92; HD VCE: RR, 0.88; 95% CI, 0.56–1.4; HD WLE with SR: RR, 1.21; 95% CI, 0.63–2.33), studies where serrated lesions were not considered (AFI: RR, 1.42; 95% CI, 0.74–2.75; HD DCE: RR, 1.91; 95% CI, 1.36–2.69; HD VCE: RR, 1.21; 95% CI, 0.75–1.95; HD WLE with SR: RR, 1.67; 95% CI, 0.95–2.94), and studies where more than one endoscopist performed trial endoscopies (AFI: RR, 1.27; 95% CI, 0.6–2.7; FUSE: RR, 3.24; 95% CI, 0.68–15.55; HD DCE: RR, 1.57; 95% CI, 1.1–2.26; HD VCE: RR, 1.18; 95% CI, 0.78–1.77; HD WLE with SR: RR, 1.45; 95% CI, 0.73–2.89) (Supplementary Figure 1).

Patients With at Least One Dysplastic Lesion Detected From Targeted Biopsies

Sixteen studies,[11,27,30,34–38,40,41,43–48] comparing a total of 6 modalities, reported this outcome and could be connected in an NMA.

The overall detection rate for HD WLE was 100 per 1000 people screened.

No modality results had high or moderate GRADE certainty.

FUSE may be no different to HD-WLE (RR, 3.24; 95% CI, 0.67–15.62; low GRADE certainty) (Figure 4*A*).

The results for HD-DCE (RR, 1.41; 95% CI, 1–1.98), HD WLE with SR (RR, 1.34; 95% CI, 0.67–2.67), AFI (RR, 1.16; 95% CI, 0.55–2.48), and HD-VCE (RR, 1.06; 95% CI, 0.72–1.55) were all of very low GRADE certainty and no conclusions can be drawn (Figure 4*A*)

Patients With at Least One Dysplastic Lesion Detected From Random Biopsies

An NMA for this outcome was not possible, as only 9 studies[11,25,27,30,34,42–44,46] with very low event numbers

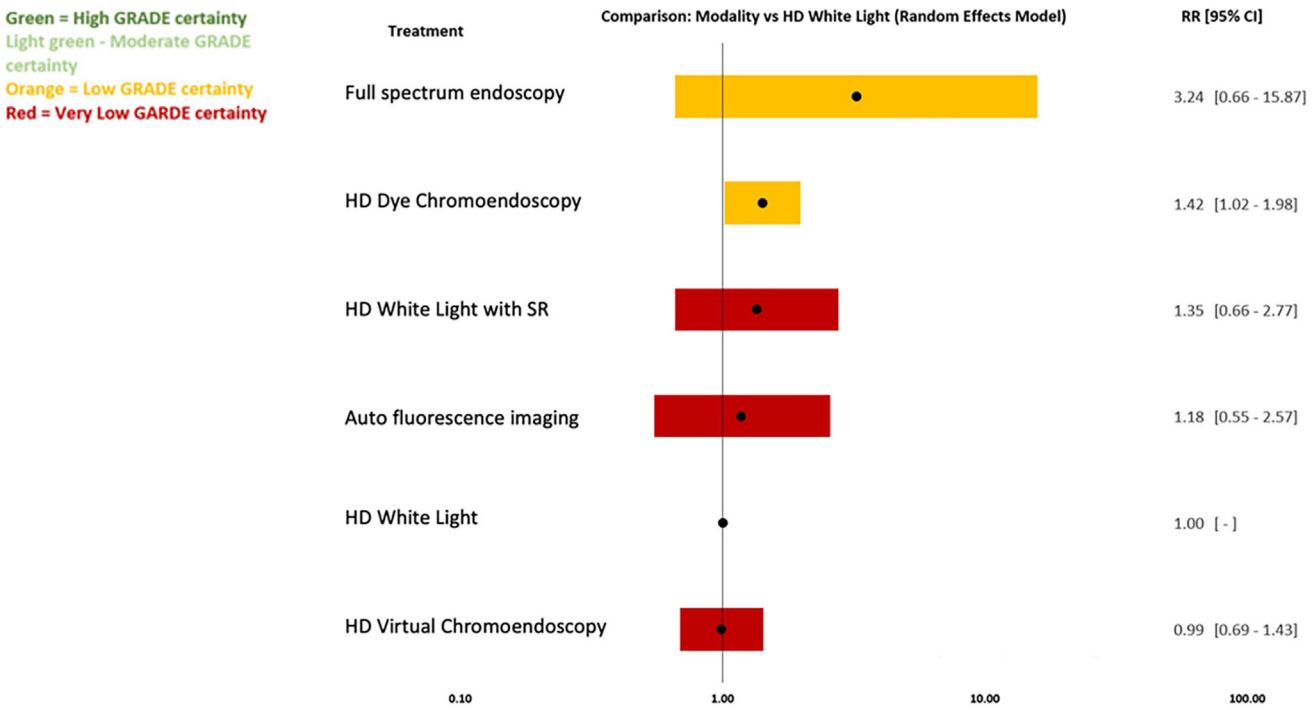

Figure 3. Forest plot and GRADE certainty for the outcome 'Patients with at least one dysplastic lesion detected' for network connected studies (n = 19).

reported outcome data, which could not be connected in a network with at least 10 studies. In total 27 participants were detected with at least one lesion from random biopsies among 3653 participants in the studies that provided outcome data.

Patients With at Least One Lesion Of Any Type Detected

Ten studies, comparing a total of 4 modalities, reported this outcome and could be connected for an NMA.[27,30,36,38–40,43–45,47] The overall detection rate for HD WLE was 187 per 1000 people screened.

No modality results had high, moderate, or low GRADE certainty.

The results for HD DCE (RR, 1.34; 95% CI, 0.89–2.01), AFI were all of very low GRADE certainty and no conclusions could be drawn (Figure 4*B*).

Patients With Serious Adverse Events

No NMA was possible for this outcome. Ten studies[11,27,30,37–40,43,45,46] reported it, of which 8 reported 0 serious adverse for their participants.[27,30,37–39,43,45,46] In total, 2 serious adverse events were reported among 2164 participants in the studies that reported this

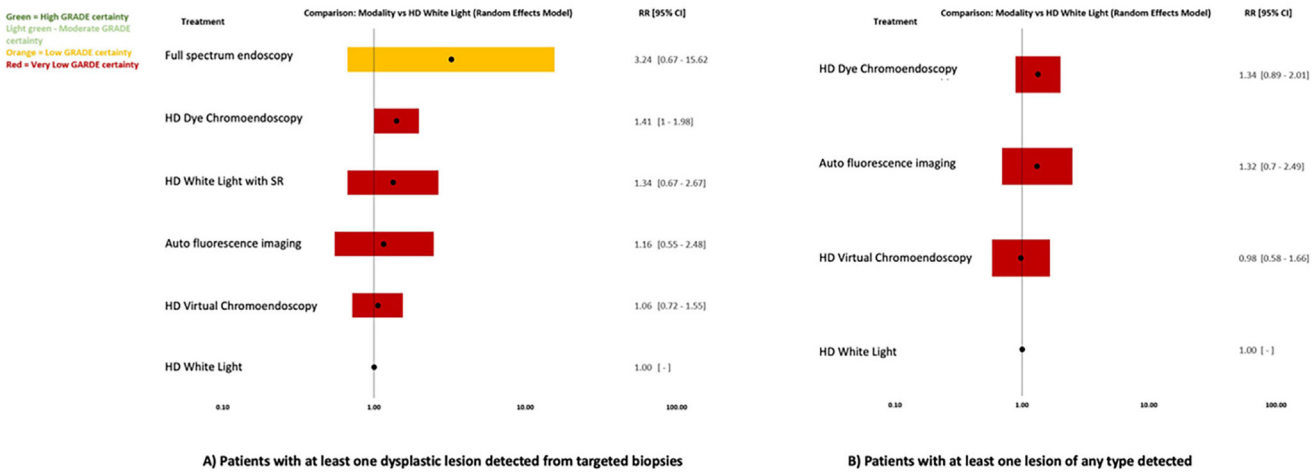

Figure 4. Forest plot and GRADE certainty for the outcomes 'Patients with at least one dysplastic lesion detected from targeted biopsies' for network connected studies (n = 16) (*A*); and 'Patients with at least one lesion of any type detected' for network connected studies (n = 10) (*B*).

Table 2. Summary of Findings Table and GRADE Decisions for the Primary Outcome of Patients With at Least One Dysplastic Lesion Detected

Patients with at least one dysplastic lesion detected						
Patient or population: people with IBD undergoing CRC surveillance						
Settings: hospital setting						
Intervention: all modalities at RCT level						
Comparison: HD white light						
	Network evidence		Anticipated absolute effects for network estimate			
Treatment	RR (95% CI)	Certainty	Detections with HD white light[a]	Detections with modality (95% CI)	% detection difference (95% CI)	Magnitude size (95% CI range of magnitude size)[b]
Full spectrum endoscopy	3.24 (0.66–15.87)	Low ⊕⊕⊖⊖	113 per 1000	366 per 1000 (75–1000)	25.3% more (3.8% less to 100%)	It may be no different to HD white light (small detection numbers less to large more).
HD chromoendoscopy (all)	1.42 (1.02–1.98)	Low ⊕⊕⊖⊖	113 per 1000	160 per 1000 (115–224)	4.7% more (0.2% more to 11.1% more)	It may detect a small amount more patients with at least one dysplastic lesion (trivial to moderate).
HD white light with SR	1.35 (0.66– 2.77)	Very low ⊕⊖⊖⊖	113 per 1000	153 per 1000 (75 to 313)	4% more (3.8% less to 20% more)	The evidence is very inconclusive.
Auto-fluorescence imaging	1.18 (0.55–2.57)	Very low ⊕⊖⊖⊖	113 per 1000	133 per 1000 (62 to 290)	2% more (5.1% less to 17.7% more)	The evidence is very inconclusive.
HD virtual chromoendoscopy (all)	0.99 (0.69–1.43)	Very low ⊕⊖⊖⊖	113 per 1000	112 per 1000 (78 to 162)	0.1% less (3.5% less to 4.9% more)	The evidence is very inconclusive.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

SUCRA	Intervention (n = 6)	Network estimate RR	Lower 95% CI	Higher 95% CI	No. of direct studies to HD-WLE	Direct GRADE	Reasons for direct downgrade	Indirect GRADE
1	Full spectrum endoscopy	3.24	0.66	15.87	1	High	No reason	X
2	HD chromoendoscopy (all)	1.42	1.02	1.98	6	Moderate	Once RoB	Moderate

Table 2. Continued

SUCRA	Intervention (n = 6)	Network estimate RR	Lower 95% CI	Higher 95% CI	No. of direct studies to HD-WLE	Direct GRADE	Reasons for direct downgrade	Indirect GRADE
3	HD white light with SR	1.35	0.66	2.77	1	Low	Twice RoB	Low
4	Auto-fluorescence imaging	1.18	0.55	2.57	1	Moderate	Once RoB	Moderate
6	HD white light	1						
5	HD virtual chromoendoscopy (all)	0.99	0.69	1.43	4	Moderate	Once RoB	Moderate

Note: Red coloring means the results cross the line of no effect.
CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HD-WLE, high-definition white-light endoscopy; N, number; RoB, risk of bias; RR, risk ratio; SR, segmental reinspection; SUCRA, surface under the cumulative ranking curve.
[a]The risk with HD-WLE has been calculated based on the cumulative HD-WLE rates of all studies with a HD-WLE arm.
[b]The range of magnitude were calculated based on the 95% CI possibility within which the actual magnitude lies, and do not imply a definitive range of benefit.

outcome: one perforation in the HD-SCE arm and one post-polypectomy bleed requiring a second therapeutic colonoscopy in the HD-DCE arm.[11,40]

Patients With Total Adverse Events

Seven studies reported all types of adverse events that occurred.[28,32,37–40,43] Five of them reported that none occurred (Yang 2019, Iacucci 16/18, Gulatti 2018, Freire 2014, van den Broek 2011).[28,32,38,39,43] In Leong 2017A, 14 patients had temporary urine discoloration, and 23 patients had transient abdominal bloating.[37] Vleugels 2018 reported 5 patients had adverse events but did not provide details of what these adverse events were.[40]

Withdrawals Due to Adverse Events

Six studies reported this outcome, with all of them reporting there were no withdrawals (Yang 2019, Iacucci 16/18, Gulatti 2018, Leong 2017A, Freire 2014, van de Broek 2011).[28,32,37–39,43]

Withdrawal Times

No NMA was possible for this outcome. In total, 20 studies[11,24,25,27,28,30,32,33,35–48] reported this outcome, in a variety of heterogeneous methods, with only 2 studies providing measures of time variance (Alexandersson 2020 and Leifield 2015);[33,44] however, numerical differences in times for HD-DCE vs HD-WLE or HD-VCE ranged from −1.1 minutes to +10.1 minutes. Details can be found in Supplementary Table 1 in the Supplementary Material.

Extracted outcome data can be found in Supplementary Table 10.

We had planned to use funnel plots to assess publication bias for pairwise analyses with at least 10 studies, but this did not occur for any outcome. Indirectness was assessed to not have occurred in any of the outcomes.

Discussion

Main Findings

Our analysis of 26 RCTs, involving 4159 participants and comparing 6 endoscopic modalities, found HD-DCE to be modality with the highest GRADE certainty level for detecting dysplasia, with a risk ratio of 1.42 (95% CI, 1.02–1.98) compared with HD-WLE. Based on our predefined thresholds, this represents a small increase in the detection of patients with at least one dysplastic lesion using HD-DCE compared with HD-WLE.

Our analysis considered key effect modifiers, such as type of IBD, colonoscopy purpose, number of endoscopists, surveillance pathway, and concurrent therapies (Supplementary Tables 1 and 10). Although factors like bowel preparation, sedation, and endoscopist experience

were inconsistently reported, no major differences in the distribution of the effect modifiers were observed. Despite some reporting heterogeneity, we believe the assumption of transitivity holds based on the available data. Subgroup analyses were performed to explore the performance of different VCE techniques (iSCAN, NBI, FICE) and dye dosages in DCE to understand each method's effectiveness in detecting dysplastic lesions[52,53]; however, these did not reveal any significant differences that would alter the overall conclusions of the NMA.

Comparison With Other Studies

Methodologically, GRADE analysis within NMAs varies significantly, affecting outcomes and interpretations.[52] Applying GRADE in NMA relies on clinical thresholds for precise judgements, but no review has consistently used these methods.[53] This inconsistency may have led to overestimations in the certainty of previous results, which was addressed in this review by pre-specifying risk thresholds set by an expert GDG. Previous NMAs and systematic reviews have highlighted the potential superiority of DCE over traditional WLE in detecting dysplasia in IBD.[13,14] Our findings align with these studies, reinforcing the argument for adopting HD-DCE in clinical practice.[15] A significant difference noted in previous reviews is in the consideration of subtypes of VCE and comparisons between VCE and DCE. El-Dallal et al conducted a meta-analysis comparing VCE with DCE (HD and SD clubbed together), SD-WLE, HD-WLE, or sub-types of VCE.[12] For the VCE category, they grouped AFI with FICE, iSCAN, and NBI. We believe that AFI should be considered separately due to its distinct mechanism of detecting natural tissue fluorescence, whereas iSCAN, FICE, and NBI enhance mucosal visualization through optical filtering or digital post-processing and can be appropriately grouped together.[8]

Recently, HD-WLE with SR has shown promising results in IBD surveillance. The HELIOS trial, a large RCT of 563 participants, demonstrated that HD-WLE with SR is noninferior to HD-DCE for detecting colorectal neoplasia (CRN) in IBD, although HD-DCE remained numerically superior.[11] This suggests that HD-WLE with SR might achieve similar neoplasia detection rates as HD-DCE, simplifying the surveillance process by eliminating the need for dye application while maintaining high detection efficacy. However, further large RCTs are needed to establish its equivalence to DCE and to confirm these findings in broader clinical practice.

Strengths and Limitations

One of the key strengths of our study is the comprehensive nature of our literature search and the rigorous application of the GRADE methodology, which enhances the reliability of our findings. Additional unpublished data were obtained through direct communication with the corresponding authors of respective studies, providing information not otherwise available. As an innovation, we employed a method of preselecting outcomes and magnitude effect thresholds for judging imprecision and that could have utility for future studies (Supplementary Table 8). These were predetermined at the beginning of the guidelines process and before the literature search by the GDG. This ensured judgements around precision by our review team were not affected by clinical bias based on awareness of the results of the analyses. The methodological rigor of our NMA was maintained by adhering to established guidelines for conducting and reporting meta-analyses.[54,55] The inclusion of only RCTs and the application of the GRADE methodology ensured a structured and transparent approach to evaluating the quality of evidence. However, the heterogeneity in study designs and the variability in reporting across the included trials posed challenges in synthesizing the data, and in turn, limits some of the scope of our analysis and conclusions. Additionally, the limited availability of safety data precluded a comprehensive analysis of the safety profiles of the endoscopic modalities. As described, certain methodological decisions were made that, although consensus-driven and believed to be objectively appropriate, do have a significant impact on the findings. For example, the exclusion of the study by Wan et al or the removal of crossover data.[56] To account for some of the impacts of these decisions, sensitivity analyses excluded studies reporting on serrated lesions, single endoscopist studies, and those based on disease activity information. These analyses were conducted to test the robustness of the primary findings considering these methodological choices.

Future Directions

Future research should focus on conducting well-designed RCTs with larger sample sizes and standardized protocols to confirm the efficacy and safety of endoscopic modalities for CRC screening in patients with IBD. Additionally, studies exploring the cost-effectiveness and environmental impact of these modalities would provide valuable insights for health care decision-making. The exploration of patient-centered outcomes and preferences in the context of CRC screening is also warranted. As the field of endoscopy evolves with new technologies and techniques, ongoing evaluation and comparison of these innovations will be essential. Emerging technologies, such as computer-aided detection (CADe) systems, require further validation in IBD populations to confirm their efficacy.[57,58] Recent studies have demonstrated that CADe systems specifically retrained with IBD images significantly improve sensitivity and specificity for detecting IBD-related neoplastic lesions.[58,59] Although initial attempts to develop artificial

intelligence systems for polyp characterization and detection in patients with IBD have shown mixed results, ongoing research aims to refine these technologies for more accurate diagnosis and surveillance in this patient population.[58–60]

Conclusions

This NMA highlights the potential advantage of HD-DCE over HD-WLE in detecting dysplastic lesions in patients with IBD undergoing CRC screening. Although HD-DCE offers enhanced detection capabilities, the low certainty of evidence and considerations of cost and environmental impact suggest prudence in its widespread adoption. Although differences for other modalities were not demonstrated, very low certainty limited conclusions, and therefore, lack of evidence should not be interpreted as evidence of no effect, indicating a need for more studies in these areas. The choice of modality should consider technology availability, endoscopist experience and training, and broader cost-effectiveness and practicality consideration.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.11.008.

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Acknowledgments
The authors thank Ore-ofeoluwa Olubusayo Adaramola and Farhad Shokraneh.

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Conflicts of interest
The authors disclose no conflicts.

Funding
Gaurav Bhaskar Nigam is funded by National Institute for Health and Care Research (Grant number 302607) for a doctoral research fellowship. James East is funded by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health.