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

**Background**

Long-standing inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), is associated with an increased risk of colorectal cancer (CRC).(1,2) As a result, regular and effective endoscopic surveillance is critical for early detection of dysplasia and prevention of CRC development in IBD patients. Various endoscopic modalities, such as high-definition (HD) white-light endoscopy (WLE), dye-based chromoendoscopy (DCE), and virtual chromoendoscopy (VCE), have been developed and tested to enhance dysplasia detection.(3) However, the relative effectiveness and safety of these techniques remain uncertain, especially in the era of high-definition imaging. This systematic review and network meta-analysis (NMA) will compare the efficacy and safety of different endoscopic modalities for colorectal cancer screening in IBD patients.

**Objectives**

* To evaluate the comparative efficacy of different endoscopic modalities in detecting dysplasia in patients with IBD.
* To assess the safety profiles of these modalities, with a focus on serious adverse events.

**Review Question**

* What is the comparative efficacy of various endoscopic modalities in detecting dysplasia in patients with IBD undergoing colorectal cancer screening?
* What are the safety outcomes associated with these endoscopic modalities?

**Methods**

***Eligibility Criteria***

**Inclusion Criteria:**

* **Population**: Patients with IBD (including ulcerative colitis, Crohn’s disease, and indeterminate colitis).
* **Intervention**: Endoscopic modalities used for dysplasia detection in IBD, including but not limited to:
	+ HD White-light Endoscopy (HD-WLE)
	+ HD Dye-based Chromoendoscopy (HD-DCE)
	+ HD Virtual Chromoendoscopy (HD-VCE)
	+ HD-WLE with segmental re-inspection
	+ Autofluorescence Imaging (AFI)
	+ Full-Spectrum Endoscopy (FUSE)
* **Comparison**: Any endoscopic modalities.
* **Outcomes**:

The BSG **Colorectal Surveillance In** IBD guideline development group pre-determined the primary and secondary outcomes as follows as part of evidence synthesis for **2024 British Society of Gastroenterology Guidelines On Colorectal Surveillance In Inflammatory Bowel Disease**:

**Primary Outcome**:

* + **Patients with at least one dysplastic lesion detected**: Defined as Vienna Classification 2 to 5 (indefinite for dysplasia, low-grade dysplasia, high-grade dysplasia, or invasive neoplasia).(4)

**Secondary Outcomes**:

* + **Patients with at least one dysplastic lesion detected from targeted biopsies**: Yield of dysplastic lesions (Vienna 2-5) from targeted biopsies during colonoscopy.
	+ **Patients with at least one dysplastic lesion detected from random biopsies**: Yield of dysplastic lesions (Vienna 2-5) from random biopsies, if taken.
	+ **Patients with at least one lesion of any type detected**: Includes both neoplastic (dysplastic + serrated) and non-neoplastic lesions (Vienna Classification 1 to 5).(4)
	+ **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 non-serious.
	+ **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 which 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 non-colitic areas.

* **Study Design**: Randomised controlled trials (RCTs)

**Exclusion Criteria:**

* Observational studies, case reports, non-RCTs, or pseudorandomised studies.
* Studies reporting on paediatric patients

***Search Strategy***

A comprehensive search will be conducted in the following databases: MEDLINE, Embase, CENTRAL, ClinicalTrials.gov, and WHO ICTRP from inception. The search will include randomized controlled trials comparing endoscopic modalities for dysplasia detection in IBD patients. Grey literature, conference abstracts, and unpublished studies will be considered. The reference lists of included studies and relevant reviews will be manually searched for additional studies.

***Study Selection***

Two reviewers will independently screen titles, abstracts, and full-text articles for eligibility. Disagreements will be resolved by discussion or by involving a third reviewer.

***Data Extraction***

Two reviewers will extract data independently using a piloted data extraction form. The extracted data will include study characteristics, patient demographics, details of endoscopic interventions, and outcomes. Risk of bias will be assessed using the Cochrane Risk of Bias tool.

**Data Synthesis and Statistical Analysis**

**Statistical analysis**

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

NMA methodology will be used as described by Higgins et al within a frequentist framework using multivariate meta-analysis.(5) We will assess the assumption of transitivity by comparing the distribution of potential effect modifiers across the pairwise comparisons. Heterogeneity will be assessed statistically using the the I2 statistic for each pairwise comparison, and with the loop-specific approach for the direct and indirect estimates. Surface under the cumulative ranking curve (SUCRA) will be used to rank treatments.

Funnel plots will be used to assess publication bias for pairwise analyses where there are at least ten studies. Indirectness will be assessed for outcomes.

Statistical analyses will be performed using the R statistical software version 4.3.1. HD-WLE will be used as the reference modality to which other modalities will be 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 IBD patients undergoing surveillance colonoscopies.(6,7)

**Subgroup and sensitivity analyses**Subgroup and sensitivity analyses will be conducted for the primary outcomes based on predefined study characteristics, such as disease severity, endoscopic modality type, and study quality, to explore potential sources of heterogeneity and to assess the robustness of the results.

**GRADE assessment for the certainty of the evidence**

The GRADE framework will be used to assess the certainty of the evidence. The direct and indirect evidence certainty will be assessed based on risk of bias, inconsistency, indirectness and publication bias. Following that the network evidence certainty will be assessed based on imprecision and incoherence, and the contribution of the direct and indirect evidence. Two review authors will independently rate the certainty ratings and disagreements will be resolved by discussion and consensus. The evidence will be rated as ‘high’, ‘moderate’, ‘low’ or ‘very low’ according to the GRADE framework. These findings will be presented in ‘Graphics on Recommendations Diagram of NMA’ plots.(8)

**Risk of Bias**

Risk of bias will be evaluated using the Cochrane tool for randomized trials. The domains assessed include random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other sources of bias. A summary of findings table will be prepared to present the GRADE assessments.

**Ethics and Dissemination**

As this study involves secondary data analysis from published literature, ethical approval is not required. The results of this systematic review and meta-analysis will be submitted for publication in a peer-reviewed journal and presented at relevant conferences.

References:

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8. Gordon M. Maintaining remission in Crohn’s disease post surgery: what can we learn from Cochrane? Frontline Gastroenterol [Internet]. 2024 [cited 2024 Jun 27];15:241–6. Available from: http://fg.bmj.com/