Meta-analysis: the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with colonic inflammatory bowel disease
Subramanian V, Mannath J, Ragunath K, Hawkey CJ

CRD summary
This review concluded that chromoendoscopy was significantly better than white light endoscopy in detecting dysplasia (all lesions and flat lesions) in patients with colonic inflammatory bowel disease. The review included only diagnostic yield studies and, given the limitations of this study design and weaknesses in review methods/reporting, the conclusions should be interpreted cautiously.

Authors’ objectives
To compare the diagnostic yield of chromoendoscopy with that of standard white light endoscopy in the detection of dysplasia or cancer in patients with colonic inflammatory bowel disease.

Searching
PubMed, EMBASE, CINAHL, Zetoc and Ingenta were searched up to February 2010 with no language restrictions; search terms were reported. Bibliographies of included studies were screened for additional articles. Only fully published studies were eligible for inclusion.

Study selection
Prospective studies that compared chromoendoscopy with white light endoscopy in patients with colonic inflammatory bowel disease, who were undergoing surveillance colonoscopy, were eligible for inclusion. Studies were required to report sufficient information for the calculation of yield of dysplasia (high or low grade) with 95% confidence intervals (CIs).

All but one of the included studies used pancolonic chromoendoscopy. Half of the studies used methylene blue dye and half used indigo carmine. Half of the included studies used multiple endoscopists. Four studies included patients with ulcerative colitis of over eight years duration (in remission). One study included patients with pancolitis over five years duration. One study included patients with extensive ulcerative colitis and Crohn's colitis involving more than one third of the colon. Most included studies were conducted in the UK or Germany, with the remainder conducted in the USA or Japan.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The methodological quality of included studies was assessed using the QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool; an overall quality score was calculated (maximum 14).

Two reviewers independently assessed methodological quality and disagreements were resolved by consensus.

Data extraction
The numbers of patients with dysplasia were extracted for each study. Calculated values were reported for the difference in proportion (with 95% confidence intervals) of dysplastic lesions identified by targeted biopsy, between chromoendoscopy and white light endoscopy. Similarly, calculated values were reported for the difference in proportion of identified dysplastic flat (non-polyloid) lesions. Calculated values (with 95% confidence intervals) were also reported for the incremental yield of chromoendoscopy over white light endoscopy in the detection of dysplasia, and for miss rates (number of dysplasias detected by random biopsy).

Data were independently extracted by two reviewers using a standard form.
Methods of synthesis
Pooled estimates of the difference in proportion of all dysplastic lesions detected by targeted biopsies, flat lesions detected, and miss rates (lesions detected by random biopsy) were calculated for chromoendoscopy compared with white light endoscopy, with 95% confidence intervals. The number of chromoendoscopy examinations required to detect one additional patient with dysplasia or cancer was calculated. A pooled estimate of weighted mean difference in the time taken for the procedure was also calculated.

Lesions classified as inconclusive for dysplasia were excluded from analyses.

Cochran's Q and $I^2$ were used to assess between-study heterogeneity. Fixed-effect models were used to pool studies unless significant heterogeneity was identified, in which case a DerSimonian-Laird random-effects model was used.

Meta-regression analysis was used to investigate possible sources of heterogeneity. Sensitivity analyses, sequentially removing studies, were used to assess the impact of individual studies on results.

Publication bias was assessed using a funnel plot and Egger's regression asymmetry test.

Results of the review
Six studies ($n=1,277$ patients, range 57 to 700) were included in the review; two studies were randomised trials, one was a prospective non-randomised trial and three were prospective cohorts. All studies had an overall QUADAS score of 11 or 12. No study provided clear reporting of uninterpretable test results or withdrawals. Half of the included studies did not report sufficient detail of the reference standard to permit replication. One study did not provide a clear description of selection criteria. The remaining QUADAS criteria were met by all studies.

The pooled incremental yield for the detection of dysplasia for chromoendoscopy over white light endoscopy was 7% (95% CI 3.2 to 11.3; six studies; $n=1,277$ patients).

The difference in the proportion of all dysplastic lesions detected by targeted biopsies was 44% (95% CI 28.6 to 59.1; six studies; $n=1,277$ patients) in favour of chromoendoscopy. The difference in proportion of flat lesions detected was 27% (95% CI 11.2 to 41.9; four studies; $n=1,118$ patients) in favour of chromoendoscopy.

Chromoendoscopy reduced the lesions detected by random biopsy by -40% (95% CI -52.8 to -27; four studies; $n=1,075$ patients) compared with white light endoscopy.

The pooled weighted difference in procedure time between chromoendoscopy and white light endoscopy was 11 minutes (95% CI 10 minutes 15 seconds to 11 minutes 43 seconds; four studies; $n=1,120$ patients).

For detection of all dysplastic lesions, meta-regression indicated that the use of magnification endoscopes, study design (patients acting as their own controls versus two separate groups undergoing chromoendoscopy and white light endoscopy), and panocolonic or targeted dye spraying in chromoendoscopy were significant predictors of yield. For detection of any dysplasia using targeted biopsies, meta-regression indicated that the dye used (methylene blue or indigo carmine), the number of endoscopists (single or multiple), study design (patients acting as their own controls versus two separate groups undergoing chromoendoscopy and white light endoscopy), and QUADAS score ($\geq12$ or $<12$) were significant predictors of yield.

Sensitivity analyses did not significantly alter results.

There was no evidence of publication bias.

Authors' conclusions
Chromoendoscopy was significantly better than white light endoscopy in detecting dysplasia (all lesions and flat lesions) in patients with colonic inflammatory bowel disease, but took longer to perform.

CRD commentary
The review stated a clear objective and defined appropriate inclusion criteria. A number of sources were searched for relevant studies, but only published studies were included. Although a test for publication bias was reported, the validity of this test has been questioned for diagnostic studies and only ten studies were included in the analysis (small numbers of studies make tests for publication bias less reliable). Consequently, publication bias could not be ruled out. The data extraction process included measures to minimise error and/or bias, but it was not clear whether similar measures were applied to study selection.

The assessment of methodological quality included a summary score (not recommended for QUADAS), although full quality assessment results were reported. The use of the QUADAS tool to assess these studies may have been misleading, as QUADAS is designed to assess test accuracy studies rather than diagnostic yield studies; criteria on the application of the reference standard were reported as positive for all studies, even though the reference standard appeared to have only been applied to test negative patients (random biopsy to determine miss rate) in four studies. In addition, although the authors stated that four studies provided data on the false positive rates for chromoendoscopy, these data were not fully reported. The meta-analytic methods used were broadly appropriate.

The authors' conclusions reflect the data presented but should be interpreted cautiously given the small number of included studies, the inherent limitations of diagnostic yield studies, and the weaknesses in review methods/reporting described.

**Implications of the review for practice and research**

**Practice:** The authors stated that chromoendoscopy could help detect dysplastic lesions and reduce need for colectomy. However, there is still a need for random biopsies as chromoendoscopy was also shown to miss some dysplastic lesions.

**Research:** The authors stated that randomised controlled trials are needed to determine whether the increased yield from chromoendoscopy translates into improved patient outcomes. They also recommended studies to compare high-definition colonoscopy with and without chromoendoscopy and to determine if the extra time needed for chromoendoscopy would improve dysplasia detection over high-definition colonoscopy. A cost effectiveness analysis, taking into account the costs of the dyes used and the spray catheter, was also suggested.

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