Title page

Long title: Feasibility and economic evaluation of chromocolonoscopy for detection of proximal serrated neoplasia: a randomised controlled trial within a population based colorectal cancer screening programme (the CONSCOP study)

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**See acknowledgments
Abstract

Background
Most post-colonoscopy interval colorectal cancers are proximal. Serrated polyps are often pre-cursors to these and considered hard to detect. We assessed the safety, feasibility and economic impact of chromocolonoscopy on detection of proximal serrated neoplasia.

Methods
A parallel group randomised controlled, open label multicentre trial (ClinicalTrials.gov: NCT01972451) within Bowel Screening Wales (BSW). Participants positive for Faecal Occult Blood were randomised 1:1 (using minimisation stratified by centre with an 80:20 random element) to either standard white light colonoscopy or chromocolonoscopy (indigo carmine dye (0·2%)) using a secure, internet-based, computerised, randomisation system that used centralised, dynamic allocation. Participants were followed up for one year and data from index colonoscopies and associated clearance procedures were analysed. All proximal polyps were reviewed by an expert pathologist panel. The study was powered to see whether or not the extra procedure time taken to conduct chromocolonoscopy was acceptable (a non-inferiority design with an inferiority margin of 15 minutes) using a per protocol analysis.

Findings
Between November 2014 - June 2016, 741 of 1031 were eligible and consented, 360 were randomized to white light colonoscopy and 381 to chromocolonoscopy. In the chromocolonoscopy arm, the procedure took an average of 6·3 (95% CIs: 4·2-8·4) minutes longer (well within the pre-specified inferiority margin of 15 minutes) but serious adverse reaction rates (two in the standard and four in the chromocolonoscopy arm with five of these being incidences of post polypectomy bleeding and one case of anxiety and hyperventilation), colonoscopy quality measures, comfort scores and sedation were similar in each arm. The proximal serrated polyp detection rate was significantly higher in the chromocolonoscopy arm.
(45/381 (11·8%) vs 23/360 (6·4%); multivariable OR 2·04, 95% CI: 1·18-3·50, p=0·010). An additional investment of £81 (95% CI: £69.91-£92.09) per procedure is required to introduce chromocolonoscopy into routine practice.

**Interpretation**

Chromocolonoscopy is feasible within a population based colorectal cancer screening programme, safe and significantly increased detection of proximal serrated neoplasia and other polyp types. Larger RCTs of chromocolonoscopy powered for improved detection of significant serrated polyps and for longer term follow up to investigate the impact on reduction of interval cancers within screening populations are warranted.

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Research in context

Evidence before this study

A systematic review of chromoscopy versus conventional endoscopy for the detection of polyps in the colon and rectum was published in the Cochrane Database of Systematic Reviews in 2016. To capture randomised trial evidence published since then, on 7 December 2018, we searched Ovid MEDLINE using: ((randomised or randomized).ab. or trial.ti. or "Clinical trial".pt. or (exp Randomized Controlled Trials as Topic/ or randomised).mp.) and ("enhanced colonoscopy" or chromoscopy or chromocolonoscopy or panchromoendoscopy or chromoendoscopy or "pan-chromoscopy" or panchromoscopy).mp. and 2014:2018.(sa_year). Titles and abstracts of 58 records were screened, and articles on narrow spectrum light/magnifying chromoendoscopy/electronic imaging/narrow band imaging/virtual chromoendoscopy/buscopan/side optic-enhancement/polypectomy technique interventions and gastric/oesophageal/Inflammatory Bowel Disease/Lynch syndrome cohorts were excluded leaving 4 studies. Of these, one was a review, one was a trial in patients with serrated polyposis syndrome only, one was a trial of the safety of oral methylene blue in 10 patients only, and one looked at the classification rather than detection of polyps.

Missed proximal serrated neoplasia may contribute to post-colonoscopy colorectal cancer. Chromocolonoscopy has been investigated in different settings and shown to increase adenoma detection rates. However, its use in the detection of proximal serrated polyps and implications for screening programmes and PCCRC has not been assessed.

Added value of this study

It is feasible to implement dye enhanced colonoscopy in a population based colorectal cancer screening program with an average 6-3 minutes of additional time taken per procedure. We
found more polyps of all types including significantly more proximal significant serrated lesions in the chromocolonoscopy group. An additional investment of £81 (95%CI: £69.9-£92.09) per procedure is required to introduce chromocolonoscopy into routine practice.

**Implications of all the available evidence**

This is the first study to demonstrate that, with rigorous trial design incorporating high quality standardised colonoscopy, chromocolonoscopy can be implemented within a population colorectal cancer screening programme with estimation of additional time and cost associated with it. It is the largest RCT of chromocolonoscopy in the detection of proximal serrated neoplasia and provides a screening population estimate of yield with minimisation of bias due to colonoscopist or pathology related factors. Further larger trials of chromocolonoscopy are warranted to look for a difference in proximal significant serrated lesion detection with full economic evaluation of follow up to assess clinical effectiveness over time and impact on clinical practice for surveillance.
Introduction

Screening has been shown to reduce colorectal cancer (CRC) incidence and mortality.¹ Studies suggest that this benefit is substantial in the reduction of distal colorectal cancers but modest for proximal colorectal cancers.²,³ Additionally, most cancers developing after an index colonoscopy, i.e. interval cancers or post-colonoscopy CRCs (PCCRCs), are located proximally.⁴ Studies have reported that interval CRC within 3 years after colonoscopy account for 3.4% to 9% of all CRCs and their incidence is associated with colonoscopy quality measures⁵,⁶ therefore individuals may be falsely reassured by screening. Two types of factors may contribute to the occurrence of proximal interval CRCs: technical (operator/procedure) dependant factors which can result in missed lesions, lower detection rates, and incomplete resection of lesions,⁷ and polyp biology dependent factors⁵,⁸ which relate to the difficulty in detection due to morphology, potential accelerated rate of growth, and molecular characteristics.⁹,¹⁰

Apart from the traditional adenoma to carcinoma pathway, it has been recognised that subsets of serrated lesions (SLs) cause cancer via an alternative pathway (serrated neoplasia pathway).¹¹ This may be responsible for up to 20% of all sporadic CRCs.¹² Several studies have also demonstrated that SLs are common precursors to proximal interval cancers.¹⁰ These polyps are flat or non-polypoid in morphology making them more difficult to detect endoscopically and studies show wide variation in detection rates (1-20%) amongst endoscopists.¹³,¹⁴ There also remains considerable variability in histopathological interpretation of serrated polyp subtypes affecting the accurate categorisation of potential precursors to the serrated pathway.¹⁵,¹⁶ This is further compounded by the existence of two different definitions of sessile serrated lesions (SSLs) promoted by the WHO¹⁷ (World Health Organisation) and the AGA¹⁸ (American Gastroenterological Association) and estimated prevalence rates vary according to
Pan-colonic chromocolonoscopy already forms part of standard practice in surveillance in high-risk cases of inflammatory bowel disease and is part of national and international guidelines. Chromocolonoscopy has been investigated in different settings and shown to increase adenoma detection rates. However, its use in the detection of proximal serrated polyps and implications for screening programmes and PCCRC has not been assessed. Technical factors affecting polyp and cancer detection rates include quality of bowel preparation, training and experience of the colonoscopist, and various procedural techniques. Colonoscopists in the UK undergo a rigorous standardised assessment and accreditation process in order to achieve high quality minimum standard criteria (e.g. adenoma detection rates, withdrawal times, comfort scores) that are monitored regularly making a UK CRC screening programme the appropriate setting to investigate chromocolonoscopy.

The aims of this study were to assess: feasibility of implementation within a population wide screening programme and of recruitment to a larger definitive trial, whether chromocolonoscopy takes an acceptable length of additional time to conduct and the associated costs, and the proximal serrated polyp detection rates (with standardised and monitored operator and procedure quality and rigorous histopathology assessment) in the trial arms to inform the sample size of a future trial.

Methods
Study design and participants
This was a multicentre, randomized, open-label, feasibility trial of dye-enhanced chromocolonoscopy vs standard white light colonoscopy. All Bowel Screening Wales (BSW)
centres were encouraged to participate in the trial. All members of the public (aged between 60 and 74 years) testing positive on Faecal Occult Blood Testing (FOBT) in the BSW programme who were eligible for an index screening colonoscopy (i.e. this excluded Polyposis syndromes, Lynch syndrome and those under regular colonoscopic surveillance for chronic inflammatory bowel disease) were assessed for trial eligibility by Specialist Screening Practitioners during telephone assessment clinics to discuss their colonoscopy. People who had undergone previous colorectal surgery, or with known allergy to food colouring agents, were excluded. Eligible people had the study described to them and, if they were interested in participating, were sent more information (including a participant information sheet and consent form) along with standard information about the screening colonoscopy. Informed consent was taken by a Specialist Screening Practitioner when the patient attended for colonoscopy, prior to the patient being told which trial arm they had been allocated to.

Randomisation and masking

All potential participants were randomised 1:1 (using minimisation stratified by centre with an 80:20 random element) to either standard or chromocolonoscopy for their index procedure using a secure, internet-based, computerised, randomisation system that used centralised, dynamic allocation. It was not possible to blind either the patient or colonoscopist to trial arm but we did blind the expert panel of three GI pathologists (see below) who classified every proximal polyp.

Procedures

Participants randomised to white light colonoscopy had a colonoscopy conducted as per standard practice. For participants randomised to the chromocolonoscopy arm, once the caecum was reached, indigo carmine dye (0.2% as used in standard clinical practice;
manufactured by Diagmed (UK)) was sprayed on the surface of the proximal colon (caecum to splenic flexure) using a pump assisted spray through the colonoscope on withdrawal. This required specific training to all the colonoscopists and Specialist Screening Practitioners to ensure standardisation of technique of dye dilution and spray as well as detection, identification and removal of polyps under indigo carmine dye. We were aware that the colonoscopists undertaking screening in this cohort were all accredited to the same standard though some had previous experience of pan-colonic dye spray use in the context of chronic inflammatory bowel disease and Lynch syndrome whereas others did not. We ensured that all participating colonoscopists attended a day long training event including quizzes of images and video prior to and after the training, a training resource for reference, as well as lectures and video tutorials on technique and lesion detection with and without indigo carmine dye spray. We also included training on the PARIS classification, Kudo classification and lesion characterisation with virtual and dye based chromocolonoscopy. In participants allocated to this arm with inadequate bowel preparation on the day, dye was used at the subsequent adequately prepared colonoscopy, otherwise repeat procedures used standard white light colonoscopy. Colonoscopists were allowed to use the irrigation pump with water for washing colonic mucosa without any restriction in both trial arms. Ten sites used high-definition colonoscopes (not mandated), one high-resolution colonoscopes and one standard definition colonoscopes. All adverse events were reported until 30 days post-colonoscopy.

Polyps retrieved from all index colonoscopies and at associated clearance procedures up to one year after were included in the analysis. Surveillance procedures were not included. Polyps found on computed tomographic colonography (CTC) undertaken for incomplete procedures, were excluded from the analysis.
Outcomes

The primary endpoint was time taken to perform the colonoscopy procedure defined as from the time when the scope was inserted to withdrawal from the anus. This, together with the data on colonoscopy outcomes, polyps found, bowel preparation, sedation, and technical quality indicators was collected by Specialist Screening Practitioners as part of routine data collection. Data on aspirin use, smoking, family history of bowel cancer, endoscopist assessment of procedural difficulty, the data in Supplementary Table S1, and data on resource use during index colonoscopy (probes, coagraspers, clips, snares, pots, etc) were not routinely collected and had to be collected on a trial specific case report.

All proximal (defined as at or above the splenic flexure) polyps included in the analysis, regardless of initial reported histology, were collected from local centres for central review by an expert panel of three GI consultant pathologists. All three were part of the national referral pathways for the bowel cancer screening programme reviews of pathology and have involvement in pathologist training and accreditation as well as regular review of “second opinion” lesions as part of a national pathology expert panel. Pre-defined standard diagnostic criteria were agreed to avoid variation in final reports and were based on the WHO classification, though serrated lesions were also categorised according to AGA criteria. In accordance with UK guidance, the term ‘sessile serrated lesion’ (SSL) was used for lesions described elsewhere as ‘sessile serrated adenoma/polyp’ (SSA/P). The expert panel reviewed all slides independently and were blinded to the original report. Cases without diagnostic agreement were re-reviewed by all three pathologists to reach a consensus diagnosis. If this was not achieved, the lesion was deemed “unclassifiable”.
An ‘advanced adenoma’ was defined as a conventional adenoma with either high grade dysplasia (HGD), >25% villous histology, or measuring ≥10mm in size. Serrated lesions (SLs) incorporated hyperplastic polyps, SSLs and traditional serrated adenomas (TSAs). ‘Significant SLs’ incorporated SSLs with dysplasia, SSLs measuring ≥10mm and all TSAs. The term ‘advanced neoplasia’ incorporated all advanced adenomas and all significant SLs.

A cost consequence analysis evaluates the costs associated with the colonoscopy procedures within the study to compare resource utilisation. The costs were assessed from the perspective of the UK NHS. Assessed in two parts, the additional costs of providing new resources required to implement chromocolonoscopy and resources used during routine practice. Implementation costs of chromocolonoscopy included additional resources in the form of staff time (both “trainee” and “trainer”) to train in the new procedure and the cost of the contrast dye and dispersion equipment. Resource use data regarding staff time performing the procedure and medications/bowel preparation administered during a procedure were collected from all participating screening sites. Resources classified as consumables were only collected from one site during index colonoscopies. Details of resource use analysis methodology can be found in the Appendix 2 of the web appendix (pages 7-12).

Statistical analysis
This feasibility study was powered to look for non-inferiority of time taken to perform the colonoscopy procedure. Experience suggested that chromocolonoscopy may take 12 minutes longer but should be no more than 15 minutes longer than standard. Assuming a common standard deviation of 15 minutes (normally distributed based on BSW data), this required 858 patients (power 90%, alpha=0·05 (one sided)) based on a two-group t-test. The protocol initially aimed to recruit 1052 patients to allow for ~18% loss to follow up for any reason.
However, the Trial Management Group decided to stop recruitment once 741 participants had been consented for the following reasons:

i) set up of some centres took longer than anticipated

ii) there was no loss to follow up after consent

iii) 741 patients still gave 86% power.

Data were analysed according to a pre-specified analysis plan using the Stata SE 14 statistical package except where indicated as post hoc in the results section. All analyses were by intention-to-treat except the analyses of colonoscopy performance (including the primary endpoint of procedure time) and technical quality indicators (Table 2 and Supplementary Table S1) which were only in those participants who had adequate bowel preparation at the index or a subsequent procedure as this is when dye was administered. The primary endpoint was assessed by calculating the 95% confidence intervals around the mean difference and comparing them to the non-inferiority margin. Proportions were compared using chi square tests. For detection rates, univariable logistic regression was used to calculate odds ratios for the trial arm effect as well as important prognostic variables (smoking, obesity, sex, family history of cancer). Multivariable models included all these variables, as well as screening centre as a random effect, using multilevel mixed-effects logistic regression. Aspirin data was only collected after the first 210 patients had been recruited and this was included in the models in sensitivity analyses. Patients found to have cancer also had polyps removed if found and we included these patients in the analyses of polyp detection rates.

The analysis of the economic data was conducted on procedures with a complete set of original data across all resource use variables and on all available cases with mean imputation for sites that did not collect data on consumables. This allowed an overall resource use comparative cost
to be calculated for all patient procedures in the available cases analysis. T-tests was used to evaluate differences in resource use costs between the two trial arms. The cost-consequence analysis provides an indication of the additional costs associated with introducing chromocolonoscopy into routine practice.

The trial protocol (ClinicalTrials.gov: NCT01972451) was approved by a UK Multi-Centre Research Ethics Committee (ref: 14/WA/0004) and was sponsored by Cardiff University.

**Role of the funding source**

Neither the funder nor the Sponsor of the study had any role in study design, data collection, data analysis, data interpretation, or writing of the report. CH, RR, and CP had full access to the raw data. SD had final responsibility for the decision to submit for publication.

**Results**

**Patients**

Between 20 November 2014 and 16 June 2016, 1031 people testing positive on FOBT, and expected to proceed to colonoscopy after discussion with a Specialist Screening Practitioner, were assessed for eligibility from 12 out of 14 centres in the BSW screening programme with 20 out of 23 colonoscopists recruiting participants (Figure 1). 903 of the 1031 people assessed were considered eligible for the trial and of these 741 (82%) consented. Consent rates after randomisation were similar in each arm: 360/416 (87%) and 381/424 (90%) with standard and chromocolonoscopy respectively. Baseline characteristics were well balanced between trial arms (Table 1). Follow up of polyps collected at later polyp clearance procedures continued until 1 year after the last participant had their index procedure.
**Procedures**

Participants in the chromocolonoscopy arm had more procedures (477 vs 427) than in the standard arm (Table 2). This was due to more repeats to remove polyps or check completeness of previous excisions in line with current guidelines. In the chromocolonoscopy arm, more participants had a final outcome of high risk (12 month) surveillance (76/381 (19·9%) vs 48/360 (13·3%); post hoc $\chi^2 = 5·812$, $p=0·016$) and fewer participants had an outcome of discharge back to routine FOBT testing (159/381 (41·7%) vs 162/360 (45·0%)).

In the first (index) colonoscopy with adequate bowel preparation, the procedure time was longer in the chromocolonoscopy arm (mean 36·8 vs 30·6 minutes) (Table 2). However, the difference did not exceed the 15 minutes specified *a priori* as the non-inferiority margin (mean difference 6·3 minutes, 95% CIs: 4·2-8·4). The data showed some evidence of positive skew, but bootstrapping produced the same estimate for the confidence interval. The magnitude of this difference was reflected in the withdrawal times (mean 24·1 vs 18·7 minutes). The difference in procedure times was smaller when no polyps were removed (mean 28·6 vs 24·2 minutes) compared to when polyps were removed (mean 41·3 vs 35·2 minutes). The bowel preparation scores, completion rates, endoscopist assessment of procedural difficulties, and procedure comfort scores were similar in each arm (Table 2).

Technical quality indicators, percentage of participants who had a position change and other manoeuvres during the procedure, and use of antispasmodic and sedation at first colonoscopy were well balanced between trial arms (Supplementary Table S1 in web appendix p1). The mean volume of fluid sprayed (diluted dye 0.2%) in the chromocolonoscopy arm was 165.8ml (SD=62.3).
Adverse events

Six Serious Adverse Reactions (SARs) were reported in the trial, two in the standard arm and four in the chromocolonoscopy arm of the trial with five of these being incidences of post-polypectomy bleeding and one case of anxiety and hyperventilation). The rates of post-polypectomy bleeding were: 1/358 (0.3%) vs 2/378 (0.5%) in the standard and chromocolonoscopy arms respectively. None of these cases required any further interventional procedures related to the bleeding. There were no allergic reactions or deaths.

Polyps

Figure 2 and Table 3 show the cancers detected and WHO classification of all polyps retrieved at index colonoscopy and associated clearance procedures up to one year afterwards. All but five proximal polyps were reviewed centrally by the expert panel. More polyps overall (903 vs 570), and more polyps of each type were found in the chromocolonoscopy arm. No patients had serrated polyposis as defined by WHO criteria though it is likely that some cases may fulfil these criteria at subsequent colonoscopy.

Detection rates for proximal SLs were significantly higher in the chromocolonoscopy arm with both univariable and multivariable analyses: 45/381 (11.8%); vs 23/360 (6.4%) univariable OR 1.96, 95% CI: 1.16-3.32, p=0.012; multivariable OR 2.04, 95% CI: 1.18-3.50, p=0.010) (Supplementary Table 2a in web appendix p2). A sensitivity analysis was conducted in the subset of patients with aspirin data (n=521) and the trial arm effect in the multivariable regression was still found to be significant (OR 1.98, 95% CI: 1.05-3.74, p=0.036), but the effect of currently taking aspirin was not (OR 1.79 in favour of taking aspirin, 95% CI: 0.72-4.50, p=0.21). We also found a significantly higher detection rate in the chromocolonoscopy arm for SLs found anywhere in the colon: 81/381 (21.3%) vs 51/360 (14.2%), multivariable
OR 1·66, 95% CI: 1·12-2·46, p=0·012. SLs were more common in smokers (multivariable OR 1·79, 95% CI: 1·00-3·22, p=0·050 for proximal SLs and multivariable OR 1·58, 95% CI: 1·03-2·42, p=0·038 for all SLs).

Secondary regression analyses compared other rates of polyp detection. While absolute polyp numbers are small there is a suggestion that detection rates of “significant” SLs anywhere in the colon were higher in the chromocolonoscopy arm (Supplementary Table 2b in web appendix p2) (multivariable OR 2·18, 95% CI: 0·88-5·37, p=0·092) and also in males (multivariable OR 3·23, 95% CI: 0·94-11·2, p=0·063). Histological criteria for distinguishing hyperplastic polyps from SSLs differ between the WHO and AGA definitions of SLs. For a diagnosis of SSL the WHO recommendations\textsuperscript{17} require two or three contiguous crypts showing characteristic SSL-type appearances whilst the AGA proposals\textsuperscript{18} require only one such crypt. Accordingly, when the AGA definition of SSL was used, 13 proximal hyperplastic polyps were re-classified as SSLs (one ≥10mm in the chromocolonoscopy arm). This marginally increased the detection rate of “significant” SLs in the chromocolonoscopy arm: 17/381 (4·5%) vs 7/360 (1·9%); multivariable OR: 2·31, 95% CI: 0·94-5·67, p=0·066). The detection rate of proximal SSLs was significantly higher in the chromocolonoscopy arm (Supplementary Table 2c in web appendix p3) (multivariable OR 1·91, 95% CI: 1·02-3·59, p=0·045), but this difference disappeared when the AGA definition of SSL was used: 34/381 (8·9%) vs 22/360 (6·1%), multivariable OR 1·58, 95% CI: 0·90-2·78, p=0·11. Higher adenoma detection rates were found in the chromocolonoscopy arm (60·9% vs 56·4% in Table 3). Analyses of advanced neoplasm detection rates suggest that obesity and male gender may be important risk factors (Supplementary Table 2d in web appendix page 3). A further multivariable analysis (data not shown) of advanced neoplasm detection rates conducted in the subset of patients with aspirin
data (n=521) in both arms of the trial combined found a significant protective effect of aspirin (23/103 (22.3%) vs 153/418 (36.6%), OR 2.11 95% CI: 1.27-3.51, p=0.004).

Of the 85 SSLs (24 in standard and 61 in chromocolonoscopy arm) identified in both arms of the study combined, six of the ten (60.0%) with dysplasia were ≥10mm compared with only 13 of the 75 (17.3%) without dysplasia (χ²=9.25, p=0.007). Surprisingly, none of the four proximal SSLs with dysplasia was ≥10mm while all six distal SSLs with dysplasia were ≥10mm.

Univariable logistic regression analysis identified statistically significant associations between the finding of any SSL and the presence of synchronous advanced adenoma(s) (OR 2.42, 95% CI: 1.19-4.93, p=0.015) and between any proximal “significant” SL and advanced adenoma(s) (OR 4.10, 95% CI: 1.01-16.7, p=0.049) in the chromocolonoscopy arm but not in the standard arm (Supplementary table S3 in web appendix p4).

**Economic evaluation**

The economic evaluation case analysis included 899 procedures (904 index and associated non-surveillance repeat procedures conducted within one year (Table 2) minus five procedures (four from the chromocolonoscopy arm and one from the standard arm) with missing data). 183 (20%) of these (91 standard arm and 92 chromocolonoscopy arm) were first procedures conducted at the site that documented the use of consumables constituted the complete case analysis. Mean training cost per procedure was £4.94 and mean equipment cost £47.99 (a total implementation cost per procedure of £52.93). A spray catheter attached to the pump was used in only 30% of procedures with a higher cost of £40 per colonoscopy. This compared to the technique used in 70% of procedures of adapting existing pumps with tubing and a valve which
added £8.88 to the cost of the colonoscopy. Supplementary Tables S4 to S6 (web appendix p5-6) show the higher costs associated with chromocolonoscopy. This is primarily due to the extra time required by staff to perform the chromocolonoscopy (£26.15 per procedure) and additional implementation costs (£52.93 per procedure). When all resource use for all procedures conducted (index and repeat Supplementary Table S4) by each arm was compared, standard colonoscopy cost per procedure was £190.60 compared to £271.60 per procedure for the chromocolonoscopy resulting in a mean cost difference of £81 (95% CI: £69.91-£92.09). Examining procedures separately produced the following results:

- Index procedures only (available cases Supplementary Table S5): mean cost difference between arms £87.68 (95% CI: 76.83-98.53) more expensive per procedure than standard colonoscopy;
- Repeat procedures only (available cases Supplementary Table S6): mean cost difference between arms £49.11 (95% CI: 11.33-86.88)

**Discussion**

Within the lack of reduction in mortality from proximal colon cancer with screening, an intervention that improves detection of proximal serrated lesions must be feasible within a screening programme and the proportion of significant proximal precursor lesions detected must be of the order that might affect surveillance and outcomes in the longer term. This study demonstrates the feasibility of recruitment of patients (82% of those eligible) and colonoscopists to a trial of standard versus chromocolonoscopy within a population based CRC screening programme. Although the procedure time took approximately 6 minutes longer in the chromocolonoscopy arm, we can be 95% confident that using chromocolonoscopy does not increase the mean time by more than 10 minutes. The dye is safe and consequent polyp detection and resection is associated with a very low rate of post-polypectomy bleeding, similar
to the standard arm. The chromocolonoscopy arm demonstrated higher detection rates for proximal serrated lesions, all serrated lesions and proximal sessile serrated lesions, and there was more advanced neoplasia and significant serrated lesions in this arm. Colonoscopy performance and technical quality indicators and patient comfort scores were similar in each trial arm whilst the additional costs of adopting the chromocolonoscopy technique would be £81 per procedure. More follow up work is required to assess the extent of further costs involved in screening surveillance as a result of improved detection.

Our study identified a number of other interesting findings. First, while dysplasia in distal SSLs only occurred in lesions ≥10mm, all proximal SSLs with dysplasia were smaller than this. This is consistent with another recent study that found the majority of proximal dysplastic SSLs to be <10mm and suggests the need for caution in setting guidelines for clinical significance based solely on the size of serrated polyps. Second, in the chromocolonoscopy arm (but not the standard arm), advanced adenomas (of conventional type) were more common in individuals harbouring SSLs. The reasons for this are unclear but the improved identification of otherwise occult SSLs by chromocolonoscopy may go some way in explaining the appearance of post-colonoscopy interval cancers in conventional screening programmes. Thirdly, there was evidence that aspirin protects against advanced neoplasia.

There is a perception that chromocolonoscopy is time consuming and this study provides quantification of the additional time taken per procedure and of the additional costs associated with chromocolonoscopy. The cost-consequence analysis provides an indication of the additional resources required to adopt this technique and shows that additional costs are primarily due to implementation. Some screening colonoscopists are already familiar with the
concept of chromocolonoscopy from their inflammatory bowel disease surveillance procedures and will consequently have less training requirements.\textsuperscript{26}

\textit{Strengths}

With 20/23 colonoscopists from 12/14 screening centres in the BSW programme participating in the current study, we demonstrate the feasibility and results from a real world programme-wide roll out of chromocolonoscopy. By contrast, previous studies have largely focused on expert centres and expert colonoscopists.\textsuperscript{27}

Previous estimates of prevalence of SLs have demonstrated significant variation possibly partly due to inconsistency in histopathological categorisation of these lesions.\textsuperscript{13,20,28} In order to address this, unlike the previous RCTs involving chromocolonoscopy, this study included an expert GI central pathology panel reviewing all slides of proximal colonic polyps.\textsuperscript{22} Randomisation was stratified by centre to ensure that any centre effects were balanced across trial arms. We demonstrated very little difference between arms in technical factors affecting mucosal visualization and consequent polyp detection and addressed most major sources of bias in previous studies due to procedure quality. To our knowledge this study is also the first to estimate the resource utilization associated with training and implementation of this intervention in routine clinical practice.

\textit{Limitations}

It is difficult to completely remove bias in chromocolonoscopy as it is impossible to blind assessors. Withdrawal times in both groups, even where polyp resection was not required, were higher than the pre-specified minimum withdrawal time of 7 minutes in the quality assurance criteria for BSW. Previous studies suggest that longer withdrawal times may improve detection
rates for serrated polyps.\textsuperscript{14,29} It may be that the dye promotes longer withdrawal times which in turn led to the higher detection rates. However, none of the previous studies suggest that a withdrawal time greater than 11 minutes would be effective in independently achieving a significant improvement in detection rates for both adenomas as well as serrated lesions supporting our findings of an independent and significant positive effect of the chromoendoscopy.\textsuperscript{30} We did not specify the use of high definition colonoscopes as a pre-requisite but data from previous studies suggests that this would be unlikely to influence the results of this study.\textsuperscript{31,32} Aspirin use was only collected for a subset of patients and the results should be treated with caution, especially in this selected screening population, although sensitivity analysis in that subset supported the main finding of the study in proximal serrated polyp detection rate. This was a feasibility study not powered to find differences in detection rates and a definitive trial with longer follow up and high definition colonoscopy mandated in both arms is planned. Finally, some variables were subject to recall bias e.g. smoking and family history of cancer/polyps.

**Conclusion**

It is safe and feasible to use index chromocolonoscopy within the CRC screening setting with an acceptable increase in procedure time of approximately 6 minutes. It is also feasible (in terms of safety, recruitment rates, procedure time, and trial logistics) to conduct a larger individually randomised trial comparing chromocolonoscopy to standard white light colonoscopy. Such a trial could be powered to find a difference in significant SSL detection rate at index since a study powered to detect a difference in PCCRC would require tens of thousands of participants. The higher proximal serrated polyp detection rates and advanced neoplasia found on chromocolonoscopy in this study contribute data to the discussion around its impact on colonoscopy quality and PCCRC.
Contributors
All authors were involved in acquisition of the data, and critical revision of the manuscript for important intellectual content. SD, CH, RR contributed to drafting the manuscript. CH performed the statistical analysis. AF and CPh performed the economic analysis. CH, SD, CPh, JS, SH, HH were responsible for the study concept and design and obtained the funding. GTW, MM and NM undertook the pathology expert review.

Declaration of interests
The authors have no competing interests to declare.

Data sharing
We do not have permission to share data from this study with other researchers. However, we can share the study protocol, statistical analysis plan, and informed consent form upon request to the corresponding author.

Acknowledgments
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Finally, we thank all patients who participated in the trial.

References


Figure 1. CONSORT diagram

Assessed for eligibility (n=1031)

Excluded (n=191)
  Ineligible (n=122)
    • Non-participating colonoscopist (n=55)
    • Colonoscopy elsewhere (n=35)
    • Surveillance (n=18)
    • Previous bowel surgery (n=9)
    • Comorbidities/unwell (n=5)
  Eligible (n=69)
    • Not interested (n=23)
    • Declined colonoscopy (n=19)
    • Worried about possible allergy/side effects (n=7)
    • Worried about possible extra time (n=3)
    • Too anxious (n=3)
    • Unable to understand (n=2)
    • Unknown reason (n=12)

Ineligible (n=122)
  • Non-participating colonoscopist (n=55)
  • Colonoscopy elsewhere (n=35)
  • Surveillance (n=18)
  • Previous bowel surgery (n=9)
  • Comorbidities/unwell (n=5)

Eligible (n=69)
  • Not interested (n=23)
  • Declined colonoscopy (n=19)
  • Worried about possible allergy/side effects (n=7)
  • Worried about possible extra time (n=3)
  • Too anxious (n=3)
  • Unable to understand (n=2)
  • Unknown reason (n=12)

Randomised (n=840)

Allocated to standard colonoscopy (n=416)

Excluded (n=56)
  Ineligible (n=2)
    • Previous bowel surgery not mentioned previously (n=1)
    • Comorbidities/unwell (n=1)
  Eligible (n=54)
    • Not interested (n=24)
    • Too anxious (n=7)
    • Declined/cancelled/did not attend colonoscopy (n=5)
    • Worried about possible extra time (n=4)
    • Worried about possible allergy/side effects (n=1)
    • Unknown reason (n=13)

Allocated to chromocolonoscopy (n=424)

Excluded (n=43)
  Ineligible (n=4)
    • Previous bowel surgery not mentioned previously (n=2)
    • Comorbidities/unwell (n=2)
  Eligible (n=39)
    • Not interested (n=19)
    • Too anxious (n=6)
    • Declined/cancelled/did not attend colonoscopy (n=1)
    • Worried about possible extra time (n=3)
    • Worried about possible allergy/side effects (n=1)
    • Unknown reason (n=11)

Consented and eligible (n=360 (87%))

Consented and eligible (n=381 (90%))
Figure 2. Flow diagram for key polyp detection rates by trial arm (ORs are given with 95% CIs with standard as the reference arm)

**Standard colonoscopy (N=360)**
- **Adenomas**
  - Anywhere
    - N=203 (56.4%)
    - Proximal
      - N=23 (6.4%)
- **Serrated**
  - Anywhere
    - N=51 (14.2%)
- **Other**
  - Anywhere
    - N=8 (2.2%)

**Chromocolonoscopy (N=381)**
- **Adenomas**
  - Anywhere
    - N=232 (60.9%)
    - Proximal
      - N=45 (11.8%)
- **Serrated**
  - Anywhere
    - N=81 (21.3%)
  - Proximal
    - N=45 (11.8%)
- **Advanced adenomas**
  - Anywhere
    - N=128 (33.6%)
    - Proximal
      - N=27 (7.1%)
- **Significant SLs**
  - Anywhere
    - N=21 (5.8%)
    - Proximal
      - N=16 (4.4%)
- **SSLs**
  - Anywhere
    - N=34 (8.9%)
    - Proximal
      - N=30 (7.9%)
- **Advanced neoplasm**
  - Anywhere
    - N=136 (35.7%)
    - Proximal
      - N=32 (8.4%)

**Advanced adenomas**

**Significant SLs**

**SSLs**

**Advanced neoplasm**

**ORs**

- **Standard colonoscopy**
  - **Adenomas**
    - Anywhere
      - N=203 (56.4%)
    - Proximal
      - N=23 (6.4%)
  - **Serrated**
    - Anywhere
      - N=51 (14.2%)
  - **Other**
    - Anywhere
      - N=8 (2.2%)

**Chromocolonoscopy**

- **Adenomas**
  - Anywhere
    - N=232 (60.9%)
    - Proximal
      - N=45 (11.8%)
  - **Serrated**
    - Anywhere
      - N=81 (21.3%)
    - Proximal
      - N=45 (11.8%)
  - **Advanced adenomas**
    - Anywhere
      - N=128 (33.6%)
      - Proximal
        - N=27 (7.1%)
    - **Significant SLs**
      - Anywhere
        - N=21 (5.8%)
      - Proximal
        - N=16 (4.4%)
    - **SSLs**
      - Anywhere
        - N=34 (8.9%)
      - Proximal
        - N=30 (7.9%)
  - **Advanced neoplasm**
    - Anywhere
      - N=136 (35.7%)
      - Proximal
        - N=32 (8.4%)
Table 1. Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Standard Colonoscopy</th>
<th>Chromocolonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=360</td>
<td>N=381</td>
</tr>
<tr>
<td><strong>Current smoking status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>37 (10.3%)</td>
<td>45 (11.8%)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>180 (50.0%)</td>
<td>196 (51.4%)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>143 (39.7%)</td>
<td>139 (36.5%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td><strong>Pack years for smoker/ex-smoker – median (IQR, n, missing)</strong></td>
<td>20 (10-39, 205, 12)</td>
<td>16 (8-34, 231, 10)</td>
</tr>
<tr>
<td><strong>Family history of bowel cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>302 (83.9%)</td>
<td>318 (83.5%)</td>
</tr>
<tr>
<td>Second degree</td>
<td>9 (2.5%)</td>
<td>13 (3.4%)</td>
</tr>
<tr>
<td>First degree</td>
<td>45 (12.5%)</td>
<td>48 (12.6%)</td>
</tr>
<tr>
<td>Both</td>
<td>3 (0.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.3%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td><strong>Family history of bowel polyps</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>340 (94.4%)</td>
<td>349 (91.6%)</td>
</tr>
<tr>
<td>Second degree</td>
<td>2 (0.6%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>First degree</td>
<td>15 (4.2%)</td>
<td>29 (7.65)</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (0.8%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td><strong>Previous abdominal/pelvic surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>96 (26.7%)</td>
<td>108 (28.7%)</td>
</tr>
<tr>
<td><strong>Presence of diverticular disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>5 (1.4%)</td>
<td>4 (1.0%)</td>
</tr>
<tr>
<td><strong>BMI – mean (SD); Obese ≥30 - n (%)</strong></td>
<td>28.8 (5.1); 134 (37.2)</td>
<td>28.9 (5.6); 128 (33.6)</td>
</tr>
<tr>
<td>Missing</td>
<td>6 (1.7%)</td>
<td>5 (1.3%)</td>
</tr>
<tr>
<td><strong>Age - median (IQR)</strong></td>
<td>67.6 (62.6-70.7)</td>
<td>67.7 (62.7-70.8)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>234 (65.0%)</td>
<td>256 (67.2%)</td>
</tr>
<tr>
<td>Female</td>
<td>126 (35.0%)</td>
<td>123 (32.8%)</td>
</tr>
<tr>
<td><strong>Aspirin data was only collected after the first 210 patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N=254</td>
<td>N=277</td>
</tr>
<tr>
<td><strong>Does the patient take daily aspirin?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently</td>
<td>52 (20.5%)</td>
<td>57 (20.6%)</td>
</tr>
<tr>
<td>Previously</td>
<td>21 (8.3%)</td>
<td>24 (8.7%)</td>
</tr>
<tr>
<td>Never</td>
<td>181 (71.3%)</td>
<td>196 (70.8%)</td>
</tr>
<tr>
<td><strong>If currently taking aspirin, what is daily dose?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75mg</td>
<td>49/52 (94.2%)</td>
<td>55/57 (96.5%)</td>
</tr>
<tr>
<td>&gt;75mg</td>
<td>3/52 (5.8%)</td>
<td>1/57 (1.8%)</td>
</tr>
<tr>
<td><strong>Missing</strong></td>
<td>0/57 (0.0%)</td>
<td>1/57 (1.8%)</td>
</tr>
</tbody>
</table>
Table 2. Index colonoscopy and associated polyp clearance procedures up to one year later (surveillance procedures not included)

<table>
<thead>
<tr>
<th></th>
<th>Standard colonoscopy</th>
<th>Chromocolonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>360</td>
<td>381</td>
</tr>
<tr>
<td>Number of procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>427</td>
<td>477</td>
</tr>
<tr>
<td>Per person rate</td>
<td>1.19</td>
<td>1.25</td>
</tr>
<tr>
<td>Number of people receiving &gt;1 procedure</td>
<td>53 (14.7%)</td>
<td>65 (17.1%)</td>
</tr>
<tr>
<td>Nature of procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index</td>
<td>360</td>
<td>381</td>
</tr>
<tr>
<td>Repeat to check completeness of polyp resection</td>
<td>26</td>
<td>33</td>
</tr>
<tr>
<td>Repeat due to incomplete previous procedure</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Repeat due to poor bowel preparation at previous procedure</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Repeat for therapeutic indication</td>
<td>28</td>
<td>55</td>
</tr>
<tr>
<td>Type of procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>399</td>
<td>430</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy</td>
<td>28</td>
<td>47</td>
</tr>
<tr>
<td>Final outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeat</td>
<td>21 (5.8%)</td>
<td>20 (5.2%)</td>
</tr>
<tr>
<td>Discharge back to routine FOBT screening</td>
<td>162 (45.0%)</td>
<td>159 (41.7%)</td>
</tr>
<tr>
<td>No further colonoscopies required due to age limit/other bowel condition</td>
<td>22 (6.1%)</td>
<td>19 (5.0%)</td>
</tr>
<tr>
<td>3 year surveillance – intermediate risk</td>
<td>64 (17.8%)</td>
<td>63 (16.5%)</td>
</tr>
<tr>
<td>12 month surveillance – high risk</td>
<td>48 (13.3%)</td>
<td>76 (19.9%)</td>
</tr>
<tr>
<td>Refer to surgery for non-cancer indication</td>
<td>2 (0.6%)</td>
<td>4 (1.0%)</td>
</tr>
<tr>
<td>Cancera</td>
<td>41 (11.4%)</td>
<td>40 (10.5%)</td>
</tr>
<tr>
<td>Inadequate bowel preparation at index then no further colonoscopies</td>
<td>2 (0.6%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>First colonoscopy with adequate bowel preparation</td>
<td>358</td>
<td>378</td>
</tr>
<tr>
<td>Number of participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowel preparation score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate</td>
<td>237 (66.2%)</td>
<td>240 (63.5%)</td>
</tr>
<tr>
<td>Excellent</td>
<td>120 (33.5%)</td>
<td>135 (35.7%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.3%)</td>
<td>3 (0.8%)</td>
</tr>
<tr>
<td>Completion rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete (caecum/ileum)</td>
<td>345 (96.4%)</td>
<td>366 (96.8%)</td>
</tr>
<tr>
<td>Incomplete (other)</td>
<td>13 (3.6%)</td>
<td>12 (3.2%)</td>
</tr>
<tr>
<td>Average procedure time (minutes) – mean (SD); median (IQR)</td>
<td>30.6 (13.7); 28 (22-36)</td>
<td>36.8 (15.0); 34 (27-45)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>When polyps removed – mean (SD); median (IQR); n</td>
<td>35.2 (14.2); 33 (25-42); 207</td>
<td>41.3 (15.2); 39 (30-50); 244</td>
</tr>
<tr>
<td>When no polyps removed – mean (SD); median (IQR); n</td>
<td>24.2 (9.8); 24 (17-28); 151</td>
<td>28.6 (10.5); 28 (21-34); 133</td>
</tr>
<tr>
<td>When endoscopist assessed procedure as difficult – mean (SD); median (IQR); n</td>
<td>41.4 (14.8); 40 (31-48); 58</td>
<td>47.4 (15.9); 44 (36-58); 66</td>
</tr>
<tr>
<td>Average withdrawal time (minutes) – mean (SD); median (IQR)c</td>
<td>18.7 (11.3); 16 (11-22)</td>
<td>24.1 (12.7); 21 (15-31)</td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>When polyps removed – mean (SD); median (IQR); n</td>
<td>23.0 (12.2); 20 (15-28); 204</td>
<td>28.5 (12.8); 25.5 (19-35); 242</td>
</tr>
<tr>
<td>When no polyps removed – mean (SD); median (IQR); n</td>
<td>12.5 (5.6); 11 (8-16); 141</td>
<td>15.4 (6.6); 15 (10-18); 123</td>
</tr>
<tr>
<td>Endoscopist assessment of procedural difficulty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>108 (30.2%)</td>
<td>106 (28.0%)</td>
</tr>
<tr>
<td>Average</td>
<td>172 (48.0%)</td>
<td>190 (50.3%)</td>
</tr>
<tr>
<td>Difficult</td>
<td>58 (16.2%)</td>
<td>66 (17.5)</td>
</tr>
<tr>
<td>Unable to complete</td>
<td>13 (3.6%)</td>
<td>12 (3.2%)</td>
</tr>
<tr>
<td>Missing</td>
<td>7 (2.0%)</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Procedure comfort score (Gloucester)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>73 (20.4%)</td>
<td>72 (19.0%)</td>
</tr>
<tr>
<td>2</td>
<td>158 (44.1%)</td>
<td>180 (47.6%)</td>
</tr>
<tr>
<td>3</td>
<td>107 (29.9%)</td>
<td>101 (26.7%)</td>
</tr>
<tr>
<td>4</td>
<td>17 (4.7%)</td>
<td>23 (6.1%)</td>
</tr>
<tr>
<td>5</td>
<td>2 (0.6%)</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.3%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

aAll repeats; bIn each arm, one found at first repeat, all others at index; cOnly recorded for complete procedures
Table 3. Polyps (WHO classification) retrieved over first and repeat procedures

<table>
<thead>
<tr>
<th></th>
<th>Standard colonoscopy (N=360)</th>
<th>Chromocolonoscopy (N=381)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of participants</td>
<td>%</td>
</tr>
<tr>
<td>No polyps or cancer</td>
<td>116</td>
<td>32.2</td>
</tr>
<tr>
<td>Cancers</td>
<td>41</td>
<td>11.4</td>
</tr>
<tr>
<td>Proximal</td>
<td>33</td>
<td>9.2</td>
</tr>
<tr>
<td>Distal</td>
<td>8</td>
<td>2.2</td>
</tr>
<tr>
<td>Number of polyps</td>
<td>n</td>
<td>per patient</td>
</tr>
<tr>
<td>Polyps (any)</td>
<td>570</td>
<td>1.583</td>
</tr>
<tr>
<td>Adenomas</td>
<td>482</td>
<td>1.339</td>
</tr>
<tr>
<td>1. HGD or villous features</td>
<td>36</td>
<td>0.100</td>
</tr>
<tr>
<td>2. Other</td>
<td>446</td>
<td>1.239</td>
</tr>
<tr>
<td>a. Other ≥ 10mm</td>
<td>122</td>
<td>0.339</td>
</tr>
<tr>
<td>Serrated lesions (SL)</td>
<td>78</td>
<td>0.217</td>
</tr>
<tr>
<td>1. Any SSL</td>
<td>24</td>
<td>0.067</td>
</tr>
<tr>
<td>a. SSL no dysplasia</td>
<td>20</td>
<td>0.056</td>
</tr>
<tr>
<td>ai. SSL no dysplasia ≥ 10mm</td>
<td>2</td>
<td>0.006</td>
</tr>
<tr>
<td>b. SSL with dysplasia</td>
<td>4</td>
<td>0.011</td>
</tr>
<tr>
<td>bi. SSL with dysplasia ≥ 10mm</td>
<td>2</td>
<td>0.006</td>
</tr>
<tr>
<td>2. TSA</td>
<td>1</td>
<td>0.003</td>
</tr>
<tr>
<td>3. HP</td>
<td>53</td>
<td>0.147</td>
</tr>
<tr>
<td>1. Mixed polyp</td>
<td>8</td>
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<tr>
<td>2. Inflammatory</td>
<td>3</td>
<td>0.008</td>
</tr>
<tr>
<td>3. Dysplasia and inflammation</td>
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<td>0.000</td>
</tr>
<tr>
<td>4. Unclassifiable</td>
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<td>0.008</td>
</tr>
<tr>
<td>Proximal SLs</td>
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<td>0.078</td>
</tr>
<tr>
<td>1. Any SSL</td>
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<td>0.050</td>
</tr>
<tr>
<td>a. SSL no dysplasia</td>
<td>16</td>
<td>0.044</td>
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<tr>
<td>ai. SSL no dysplasia ≥ 10mm</td>
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<td>0.003</td>
</tr>
<tr>
<td>b. SSL with dysplasia</td>
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</tr>
<tr>
<td>bi. SSL with dysplasia ≥ 10mm</td>
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<td>0.000</td>
</tr>
<tr>
<td>2. TSA</td>
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<td>0.000</td>
</tr>
<tr>
<td>3. HP</td>
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<tr>
<td>&quot;Advanced neoplasia&quot;</td>
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<tr>
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<td>0.125</td>
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<tr>
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<tr>
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<tr>
<td>Overall</td>
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<tr>
<td>Proximal</td>
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<tr>
<td>&quot;Significant SLs&quot;</td>
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<td>0.001</td>
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<tr>
<td>Overall</td>
<td>39</td>
<td>10.8</td>
</tr>
<tr>
<td>At least one SL and adenoma</td>
<td>39</td>
<td>10.8</td>
</tr>
</tbody>
</table>

a One polyp in standard arm was advanced, two in chromo colonoscopy arm were advanced
b Advanced adenoma or “Significant SL” or advanced mixed polyp
c HGD or villous features or ≥10mm
d SSL with dysplasia or any SSL≥10mm or TSA