Chromoendoscopy versus standard colonoscopy for detection of nonpolypoid dysplasia in patients with inflammatory bowel disease

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ABSTRACT

AIM: Inflammatory bowel disease (IBD) is associated with an increased risk of colorectal cancer. Studies show that chromoendoscopy (CE) can increase the detection of dysplasia at surveillance colonoscopy, compared to standard white light endoscopy (WLE). We performed a retrospective cohort study to compare standard WLE to CE with targeted biopsies in detecting nonpolypoid dysplasia in IBD patients undergoing surveillance colonoscopy at a single tertiary centre.

METHOD: Data was collected on 110 consecutive patients with IBD who underwent surveillance colonoscopy from 1 August 2015 to 31 July 2017 at Counties Manukau District Health Board, Auckland. Patients had either WLE or CE. Patient characteristics, endoscopic and histologic descriptions were reviewed. Rates of dysplasia detection by the different endoscopic techniques were compared using an exact Poisson test.

RESULTS: 76/110 (69%) had WLE (mean age 56y; median disease duration 18y) and 34/110 (31%) had CE (median age 59y; median disease duration 19y). Nonpolypoid dysplasia was detected in 0/76 (0%) patients who had WLE. Seven nonpolypoid dysplastic lesions were detected in 4/34 (11.8%) patients who had CE. Dysplasia pick up rate was significantly higher in the CE group with a risk difference of 11.8%, 95% confidence interval (0.93, 22.59), p=0.008. Dysplasia detection rate per patient was also significantly higher in the CE group with a rate difference of 20.6 lesions per 100 patients, 95% confidence interval (5.3, 35.8), p=0.0003. As expected, there was no difference between the number of polypoid dysplastic lesions found between the two groups (p=0.12).

CONCLUSION: In our cohort of IBD patients undergoing surveillance colonoscopy, CE with targeted biopsy is associated with a significantly increased nonpolypoid dysplasia detection rate when compared to WLE. These results are comparable to studies performed in the rest of the world.

Patients with chronic inflammatory bowel disease (IBD) are at increased risk of colorectal cancer (CRC). IBD is the third-highest risk factor for CRC.[1] The cumulative probability of development of CRC in ulcerative colitis (UC) is estimated at 2% by 10 years, 8% by 20 years and 18% by 30 years.[2] Compared to sporadic CRC, these patients may have a higher histologic grade[3] with greater mortality,[4] accounting for one-sixth of deaths in IBD patients.[5] In New Zealand, this risk is reflected in our national guideline for Surveillance for People at Increased Risk of Colorectal Cancer,[6] which recommends one-, three- or five-yearly intervals for colonoscopic surveillance depending on additional risk factors.

Chromoendoscopy (CE) describes the segmental, topical application of 0.4% indigo carmine or 0.1% methylene blue dye onto colonic mucosa. This provides contrast enhancement to improve detection and visualisation of subtle colonic lesions which may be flat, not easily visible with regular white light endoscopy (WLE) used during

standard colonoscopy. Reference to CE was removed from the national guidance statement[6] as it was not available at the time in New Zealand. The alternative option recommends quadrantic random biopsies every 10 centimetres. Critics of this method note that it may only sample 0.03% of the mucosal surface from the recommended minimum 33 biopsies and has a dysplasia detection rate of <2 per 1,000 biopsies.[7] In addition, many clinicians did not follow this protocol.[8,9] This has led to a transition to CE which is associated with a 7% greater yield in detecting nonpolypoid dysplasia, a 40% lower miss rate compared to WLE[10] and greater proportions of detected neoplasia.[11,12] CE also has similar withdrawal times and requires fewer biopsies taken overall, improving efficiency and cost effectiveness.[13–15] Current society guidelines have updated their approach in light of this evidence to include a preference for CE.[16–19] Despite this, there has been some reluctance within the gastroenterology community to take up CE,[20] with some studies suggesting little benefit, [21–26] adding to clinical equipoise and debate about its utility. Variance in study results may be attributed to local expertise and experience with differences in practice, newer high-definition scopes and use of virtual chromoendoscopy with narrow band imaging (NBI). Newer imaging technologies such as NBI, i-Scan[24] (electronic staining) or Fuji Intelligent Color Enhancement[27] (FICE) technology may increase lesion detection rates further. No local data exists from New Zealand on nonpolypoid dysplasia detection rates for CE as compared to standard colonoscopy.

Methods

We retrospectively collected data on 110 consecutive patients with IBD who underwent surveillance colonoscopy from 1 August 2015 to 31 July 2017 at Counties Manukau District Health Board. Colonoscopies were classified as a surveillance procedure when the endoscopy report explicitly stated this as the indication for the procedure.

We targeted a total number of 35 and 70 participants under CE and WLE respectively as a compromise between feasibility and power. First, these recruitment figures appeared achievable in two years of data collection. Secondly, the 1:2 proportion reflected the relative availability of endoscopists trained vs not trained to perform CE. Finally, simulations using a Poisson model and a grid of relative rates showed that these numbers were sufficient to detect a relative rate of detection of 9 between CE and WLE with 80% power at a 5% significance level against a two-sided alternative, under the assumption that two lesions per 100 participants be detected under WLE as per Rutter et al.[13] Although this was a high detectable relative rate, local experience indicated that it was plausible.

Patients had surveillance with either WLE or CE at the endoscopists' discretion. All endoscopists were gastroenterology consultants experienced in colitis surveillance. A single operator (AS) completed the majority (27/34) of the CE cases. Targeted biopsies were taken in the CE group and random quadrantic biopsies every 10cm with additional targeted biopsies in the WLE group. Colonoscopy was carried out primarily using standard Olympus colonoscopes (CF-H190I series). CE was completed with either 0.1% methylene blue or 0.4% indigo carmine, and distributed using the waterjet channel using the auxiliary foot pump. The dye was sprayed in a segmental fashion and excess dye was suctioned before visual examination. Biopsy specimens were processed according to standard procedures and read by gastrointestinal pathologists. Patient demographics, relevant background, endoscopic and histologic descriptions were reviewed from the computerised clinical and endoscopic database.

The primary endpoint was the number of patients with nonpolypoid dysplastic lesions detected. The secondary endpoint was the number of polypoid dysplastic lesions detected.

Baseline age at colonoscopy was compared between the two modalities using Wilcoxon's two-sample test. Baseline categorical variables between the two modalities were compared using Fisher's exact test, producing an observed significance level. Duration of disease was compared between the two modalities using the log-rank test. Rates of dysplasia detection by the different endoscopic techniques were compared using an exact Poisson test.

Results

One hundred and ten IBD surveillance colonoscopies were reviewed, including 76 (69%) who had WLE and 34 (31%) who had CE. The mean age was 56 years old (Standard Deviation 14), with the median duration of disease 18 years (IQR 16.5). 43/76 (57%) in the WLE cohort had UC, compared with 22/34 (65%) in the CE cohort. Fifty-eight percent of patients had pancolitis, with the majority having no (51%) or mild (34%) inflammation. The groups were well-matched for all demographic and colonoscopic variables that were collected (Table 1).

Seven nonpolypoid dysplastic lesions were detected in 4/34 (11.8%) patients, all in the CE group (Table 2). Five lesions had low-grade dysplasia and two had high-grade dysplasia. There were no invasive cancers. Five were dysplasia with tubular architecture and two had serrated dysplasia (Table 3). None were detected using WLE. This pick-up rate was significantly higher in the CE group with a risk difference of 11.8%, 95% Confidence Interval (CI) [0.9–22.6], p=0.008. Nonpolypoid dysplasia detection rate per patient was also significantly higher in the CE group with a rate difference of 20.6 lesions per 100 patients, 95% CI [5.3-35.8], p=0.0003.

Table 1: Patient and colonoscopy information for WLE and CE.

Characteristic	**All cohort (n=110)**	**WLE (n=76)**	**CE (n=34)**	**p-value**
Age, mean years	56	55	58	0.26
Male gender, n (%)	59 (46)	42 (45)	17 (50)	0.68
Ulcerative colitis or Crohn's disease				
Ulcerative colitis, n (%)	64 (59)	43 (57)	22 (65)	0.53
Crohn's disease, n (%)	45 (41)	33 (43)	12 (35)	
Duration of disease				
Median (years)	18	18	19	0.88
<8 years, n (%)	15 (13)	11 (14)	4 (12)	0.96
8–15 years, n (%)	25 (23)	18 (24)	7 (21)	
15–25 years, n (%)	35 (32)	24 (32)	11 (32)	
25+ years, n (%)	35 (32)	23 (30)	12 (35)	
Disease extent				
Pancolitis, n (%)	64 (58)	41 (54)	23 (68)	0.16
Left-sided colitis, n (%)	18 (16)	13 (17)	5 (15)	
Right-sided colitis, n (%)	1 (1)	0 (0)	1 (3)	
Ileocolonic Crohn's disease, n (%)	27 (25)	22 (29)	5 (15)	
Family history of bowel cancer, n (%)	1 (1)	0 (0)	1 (3)	0.31
Primary sclerosing cholangitis, n (%)	5 (5)	5 (7)	0 (0)	0.32
Mucosal inflammation				
None, n (%)	56 (51)	36 (47)	20 (59)	0.64
Mild, n (%)	38 (34)	27 (36)	11 (32)	
Moderate, n (%)	15 (14)	12 (16)	3 (9)	
Severe, n (%)	1 (1)	1 (1)	0 (0)	

Table 2: Nonpolypoid and polypoid dysplastic lesions found for WLE and CE, patient frequency and lesion counts.

	All cohort (n=110)	WLE (n=76)	CE (n=34)	p-value
Nonpolypoid dysplastic lesions				
Patients with nonpolypoid dysplastic lesions detected, n (%)	4 (4)	0 (0)	4 (12)	0.008
Number of nonpolypoid dysplastic lesions	7	0	7	0.0003
Polypoid dysplastic lesions				
Patients with polypoid dysplastic lesions detected, n (%)	14 (13)	7 (9)	7 (21)	0.12
Number of tubular adenoma detected	14	7	7	0.41*
Number of tubulovillous adenoma detected	6	6	0	
Number of sessile serrated adenoma detected	8	4	4	

*p-value comparing total number of lesions detected (17 for WLE vs. 11 for CE).

As expected, there was no difference between the number of polypoid dysplastic lesions found between the two groups (p=0.12). One patient with pancolitis was discovered to have a neuroendocrine tumour using WLE. No other malignancy was identified.

Discussion

This study demonstrates that in our setting, use of CE with targeted biopsies for colonoscopic surveillance in IBD is associated with a higher nonpolypoid dysplasia detection rate as compared with WLE. These findings are similar to those found in international studies with a meta-analysis[10] of six prospective studies involving 1,277 patients demonstrating a difference in yield of nonpolypoid dysplasia between CE and WLE of 7% (95% CI 3.2–11.3).

With the rising incidence of IBD both internationally[28] and in New Zealand,[29,30] it is vital for both general physicians as well as colonoscopists to be aware of CRC risk and appropriate and timely referral to enter into surveillance programs. Previously, New Zealand colonoscopists demonstrated poor understanding of the importance of

Table 3: Histology and location of nonpolypoid lesions identified on CE.

Patients with nonpolypoid lesions (n=4)	No. of lesions (n=7)	Location	Paris classification	Histology
Patient 1	1	Ascending colon	0-IIa	Low-grade serrated dysplasia
Patient 2	1	Ascending colon	0-IIb	High-grade serrated dysplasia
Patient 3	1	Sigmoid colon	0-IIa	Low-grade dysplasia with tubular architecture
Patient 4	4	Ascending colon	0-IIa	Low-grade dysplasia with tubular architecture
		Hepatic flexure	0-IIa	Low-grade dysplasia with tubular architecture
		Sigmoid colon	0-IIb	High-grade dysplasia with tubular architecture
		Rectum	0-IIa	Low-grade dysplasia with tubular architecture

dysplasia associated with colitis.[9] There was also variance in surveillance practice, both timing of procedure and biopsy protocols, which will only compound the technical and practical limitations of dysplasia detection outlined in this paper.

The clinical implications of this study, although not able to be formally addressed by this study design, include the potential for increased targeted endoscopic resection of the identified dysplastic lesions. In addition to close follow-up, this treatment method has been shown to be a safe alternative to colectomy in selected patients.[31,32]

The retrospective nature of the study, with its inherent limitations restricts interpretation with potential for confounders and bias. However, this study demonstrates real-life practice of surveillance methods at our centre, with endoscopists left to decide based on their clinical judgment which method to use. The lack of randomisation may lead to differences in patient characteristics, yet pseudo-randomisation by enrolment of consecutive patients apparently matched all measured variables between the two groups, allaying the likelihood of confounding. Further limitations include potentially important non-measured variables such as the patients IBD treatment modalities, bowel preparation scores and previous surveillance outcomes.[6] We also did not record data on number of biopsies, time taken for procedure and the potential cost implications of these, although CE is thought to be overall less costly than WLE.[15]

One endoscopist (AS) performed 27/34 (79%) of the CE procedures. This may have introduced selection bias, with more difficult or higher-risk patients being referred to this procedure list. All endoscopists who completed CE in this study were already experienced with this modality. No learning curve was taken into account. However, studies have presented data demonstrating no difference between expert (performed >20 CE-based dysplasia surveillance procedures) and non-expert endoscopists for dysplasia detection.[23] The multiple operators in this study introduce risk of inter-observer variability, but allows for real-world results.

In conclusion, CE with targeted biopsy is associated with a significantly increased nonpolypoid dysplasia detection rate when compared to WLE for dysplasia surveillance in patients with IBD. With the accumulated high-quality international evidence, subsequent international societal guidelines and similar findings from this retrospective study in our local setting, CE certainly warrants consideration of incorporation into the next New Zealand CRC surveillance recommendations for patients with IBD.

Competing interests:
Nil.

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