

Title:

Diagnostic yield of dysplasia in polyp adjacent biopsies for patients with inflammatory bowel disease:
A cross-sectional study

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Abstract

Introduction:

Patients with inflammatory bowel disease (IBD) undergoing polypectomy are recommended by current guidelines to have biopsies taken from the adjacent mucosa to determine whether there is dysplasia present. With improvements in endoscopic imaging technology it is now possible to characterise colonic lesions with higher levels of confidence than previously. We reviewed the diagnostic yield of such adjacent biopsies.

Materials and Methods:

A systematic search of our histopathology database revealed cases where polyps had been endoscopically resected or biopsied in patients with IBD. Endoscopy reports and medical records were reviewed and patient demographic and disease specific details were recorded, along with details of polyp characteristics and histopathology outcomes.

Results:

Three hundred and two polyps were biopsied or resected in 131 patients undergoing 178 colonoscopies. Median polyp size was 4mm (range 1-45) and the predominant morphology was Paris 0-Is (n=98, 32%). Histology was tubular adenoma in 76 (25%), tubulovillous adenoma in 14 (5%), hyperplastic in 112 (37%), post-inflammatory in 32 (11%), sessile serrated polyp in 31 (10%), traditional serrated adenoma in 2 (0.7%), flat high-grade dysplasia or cancer in 2 (0.7%) and other in 33 (11%). Dysplasia in adjacent biopsies was detected in 2 patients (0.7%) and was endoscopically visible in both cases. The proportion of endoscopically unsuspected dysplasia was 0/300 (0%, 95% CI 0-1.6%).

Conclusion:

The diagnostic yield for polyp adjacent biopsies in patients with IBD is negligible. With high definition technology and chromoendoscopy it may no longer be necessary to biopsy endoscopically normal adjacent tissue to detect invisible dysplasia.

Introduction

Patients with inflammatory bowel disease (IBD) undergoing endoscopic polypectomy are recommended by international consensus guidelines from the European Crohn's and Colitis Organisation (ECCO), American Gastroenterology Association (AGA) and the North American SCENIC group (Farraye, Odze et al. 2010, Annese, Daperno et al. 2013, Laine, Kaltenbach et al. 2015) to have biopsies taken from the area immediately adjacent to the resected polyp. The aim of these adjacent biopsies is to detect endoscopically non-visible dysplasia. This recommendation is not strongly evidence based. Histopathology guidelines (Magro, Langner et al. 2013) also support this practice, however no guideline describes a clear protocol and there is no recommendation as to the number of biopsies or the distance from the resected lesion. The concept of taking polyp adjacent biopsies has arisen from the increasingly historical concept of distinguishing an adenoma-like mass (ALM) from a dysplasia associated lesion or mass (DALM). This terminology has been discouraged by contemporary guidelines (Laine, Kaltenbach et al. 2015) in favour of a shift toward use of the more helpful distinction between visible, circumscribed dysplasia and endoscopically invisible dysplasia, previously described as "flat" dysplasia.

It is now apparent that the risks of advanced neoplasia and colorectal cancer (CRC) in patients with colitis may have been overstated in the past (Velayos, Kathalia et al. 2017). While large cohort studies have shown increased dysplasia detection over recent years (Choi, Rutter et al. 2015), colitis associated CRC rates appear to be reducing in patients undergoing surveillance (Choi, Rutter et al. 2015, Fumery, Dulai et al. 2016). Whether this is due to improved medical therapy and reduced cumulative inflammation over the course of patients' illness, more representative population based cohorts, or a true effect of active surveillance remains unclear.

The true natural history of low-grade dysplasia in colitis is poorly understood but it appears that carefully resected sporadic lesions, particularly those of smaller (<10mm) size and sessile or pedunculated (Paris 0-I) appearance may not carry a significantly heightened long term CRC risk (Wanders, Dekker et al. 2014, Choi, Ignjatovic-Wilson et al. 2015, Kisiel and Loftus 2015). Other clinical risk factors clearly need to be considered when deciding upon subsequent surveillance intervals,

such as duration and extent of disease, historical inflammatory burden, presence of multiple post-inflammatory polyps and family history of CRC (Cairns, Scholefield et al. 2010).

Studies examining the diagnostic value of polyp adjacent mucosal biopsies are limited however a recent study from the Netherlands (Ten Hove, Mooiweer et al. 2017) supports a low diagnostic yield and importantly the absence of any significant impact upon clinical outcomes in patients where adjacent biopsies have shown dysplasia.

Historically, colonic assessment and surveillance in IBD patients has been limited by technology, poor endoscopic views and physician concerns in relation to missed lesions (Velayos, Kathpalia et al. 2017). Endoscopists have therefore relied upon histology as a gold standard technique for dysplasia detection. Until recently (and still in the absence of the availability of advanced techniques (Annese, Daperno et al. 2013) it had been recommended to take random quadrantic biopsies every 10cm when performing surveillance in colitis patients. Pan-colonic dye spray (chromoendoscopy), with or without high definition imaging, is now recommended as the gold standard technique for surveillance in IBD and is associated with enhanced neoplasia detection (Rutter, Saunders et al. 2004). Further, it appears that, even with standard definition modern video endoscopes, most dysplasia is endoscopically visible (Rutter, Saunders et al. 2004). The suggestion from the SCENIC consensus (Laine, Kaltenbach et al. 2015) is that with appropriate training and use of readily available advanced techniques, circumscribed lesions can be accurately characterised with a high level of confidence and can then be resected with patients undergoing close subsequent endoscopic surveillance. Risk of cancer progression for colitis associated lesions is estimated to be 14 cases per 1000 years of patient follow-up (Thomas, Abrams et al. 2007). The risks associated with resected sporadic lesions are considerably less (Wanders, Dekker et al. 2014) and evidence suggests that these can be safely managed by standard polypectomy and surveillance (Rubin, Friedman et al. 1999, Vieth, Behrens et al. 2006, Kisiel, Loftus et al. 2012) but it remains unclear whether adjacent mucosal biopsies are helpful in determining future risk. With a move away from random biopsies to a more targeted approach now being adopted in the context of surveillance, our hypothesis for this study was that polyp adjacent biopsies may no longer be necessary when performing polypectomy in patients with IBD.

Materials and Methods

We reviewed the diagnostic yield of polyp adjacent biopsies in patients with IBD over a recent five-year period at a large NHS University Hospital Foundation Trust. This included patients from a tertiary academic university teaching hospital with subspecialty interests in IBD and therapeutic endoscopy, and also patients from a smaller district general hospital. Ethical approval for the study was applied for and granted by the Trust Research Ethics Committee as a clinical practice audit.

A systematic search of our histopathology database, using search terms “dysplasia”, “DALM”, “chronic colitis” and “chronic proctocolitis” for the period between January 2010 and December 2015 revealed cases where polyps had been endoscopically resected or biopsied in patients with IBD. Inclusion criteria were patients with a diagnosis of chronic IBD, either ulcerative colitis (E1, E2 or E3), colonic Crohn’s disease (L2) or IBD-unclassified, who were undergoing endoscopic assessment of their disease activity, or surveillance. Exclusion criteria were patients who did not have a diagnosis of IBD, or those who had undergone colectomy with ileo-pouch-anal anastomosis (IPAA). Endoscopy and histopathology reports as well as electronic patient records were reviewed and patient demographic and disease specific details were recorded, along with details of polyp characteristics and histopathology outcomes. Search methods and numbers of exclusions are further detailed in figure 1. Descriptive statistics were reported using Vassar Stats (www.vassarstats.net). Sensitivity analyses were carried out to determine the impact of procedural and operator related variables on the diagnostic yield from polyp adjacent biopsies. This study is reported according to the STROBE guidelines (von Elm, Altman et al. 2007).

Results

Between 2010 and 2015, 302 polyps were biopsied or resected in 131 patients undergoing 178 colonoscopic examinations over two hospital sites.

Patient demographic, disease specific and procedural data in relation to polyps resected are presented in table 1. Median patient age was 60 (range 17-82), with 43% female. One hundred and twenty-three patients (92%) had ulcerative colitis, with the majority pan colitis (E3). Six patients had Crohn's colitis and 2 IBD-unclassified. Thirty patients (23%) had PSC. Median disease duration was 20 years (range 1-58 years). The majority of patients (52%) were on ASA based monotherapy (data not shown).

On a per-procedure analysis (n=178), 71 patients (40%) underwent chromoendoscopy, while 49 (28%) had their examinations with a high-definition colonoscope. Endoscopic inflammation was recorded in 77 (43%), with post-inflammatory polyps in 36 (20%) and histological evidence of active inflammation in 39 (22%).

On a per polyp analysis (n=302, figure 2), histology was tubular adenoma in 76 (25%), tubulovillous adenoma in 14 (5%), hyperplastic in 112 (37%), post-inflammatory in 32 (11%), sessile serrated polyp in 31 (10%), traditional serrated adenoma in 2 (0.7%), flat high-grade dysplasia or cancer in 2 (1%) and other in 33 (11%).

Median polyp size (table 2) was 4mm (range 1-45). The degree of dysplasia in polyps was low grade in 89 patients (29%), high grade in 5 (2%). Cancer was found in one lesion (0.5%). The predominant morphology was Paris 0-Is (sessile, n=98, 32%), followed by 0-IIa (flat elevated, n=73, 24%). Polyp location was above splenic flexure in 162 (54%).

Adjacent biopsies were those either clearly stated on the endoscopy report (n=68, 23%) or from within the same bowel segment as the polyp (n=161, 53%). Inflammation in adjacent biopsies was present in 34 patients (11%). Dysplasia in adjacent biopsies was detected in 2 patients (0.7%) and was endoscopically visible in both cases (figure 3). The proportion of endoscopically unsuspected dysplasia revealed by adjacent biopsies was 0/300 (0%, 95% CI 0-1.6%).

A sensitivity analysis (table 3) was carried out for the procedures where dysplasia was detected (n=71) for factors which may have influenced either the likelihood for adjacent biopsies to be taken, or for those biopsies to yield dysplasia. Analyses for tertiary vs. district general hospitals, IBD specialist vs.

non-specialist endoscopists, chromoendoscopy vs. white light and high definition vs. standard definition endoscopes did not show any difference in terms of these two outcomes.

Median duration of follow up was 29 months (range 0-79). During our period of follow-up 6 patients underwent colectomy, including two for CRC, one for HGD (CRC in colectomy specimen), two for multifocal LGD and one for medically refractory colitis. In the two patients where polyp adjacent dysplasia was found (figure 3), both patients were recommended to undergo colectomy and one patient (C) had cancer.

Discussion

Our data suggests that the diagnostic yield for polyp adjacent biopsies in IBD is negligible. In fact, the yield for unexpected dysplasia was zero in our cohort, as both lesions where dysplasia was detected in adjacent biopsies were clearly endoscopically suspicious. Other data, although limited to a single study, supports a similar conclusion to ours and further suggest that there is no longitudinal clinical prognostic value in carrying out adjacent biopsies (Ten Hove, Mooiweer et al. 2017). The Dutch study was carried out in a referral centres and focused on patients participating in a surveillance programme. Our study relates to both tertiary referral and a smaller district general hospital, and also includes a spectrum of endoscopic training and expertise. It appears from our analysis that these factors, as well as higher level advanced endoscopic techniques, although expected to be helpful in aiding careful assessment and resection of lesions, are not essential. Even with standard definition technology and more general gastroenterology practice, adjacent biopsies were not clinically useful. Nonetheless it is clear from other data that dysplasia detection is enhanced when “second look” colonoscopy is performed at a specialist centre after referral from elsewhere (Rubin, Krugliak Cleveland et al. 2016). In keeping with SCENIC recommendations (Laine, Kaltenbach et al. 2015), we suggest that where the extent or resectability of a lesion is unclear, referral to a specialist IBD endoscopist should be standard.

The concept of field cancerization suggests that molecular or epigenetic changes can occur throughout the intestinal epithelium in patients with IBD and significantly increase the risk of CRC developing (Leedham, Graham et al. 2009, Galandiuk, Rodriguez-Justo et al. 2012). These molecular changes can occur early and in fact have been shown to pre-date the development of dysplasia. It is therefore possible that, due to sampling error or other factors, negative adjacent biopsies may provide a false sense of security in the stratification of future neoplastic risk for individual patients and it may be that molecular changes are a better marker of risk for IBD-associated neoplasia. We await development and validation of reliable and reproducible assays that may in future allow us to better risk stratify patients with colitis associated neoplasia and those undergoing surveillance to determine more individualised management strategies.

Our study has several strengths, including representing a heterogeneous cohort of IBD patients over a long period of time with close clinical follow up. Of course the retrospective nature of the study is a

limitation and perhaps a longitudinal, registry-type study or prospective randomised trial will ultimately be required to address this question definitively. The rate of non-biopsy in our study was high but consistent with other data(Ten Hove, Mooiweer et al. 2017) and this may imply a shift in practice for physicians who are already selecting out less suspicious lesions and not performing adjacent biopsies. Unfortunately, our endoscopy reporting system did not have a designated field for adjacent biopsies and so we included both clearly stated polyp adjacent biopsies (free text) and those where biopsies were taken from the same segment as the polyp. This approach, while potentially over-estimating our denominator, was intended to ensure that no potentially significant cases were missed. A separate analysis (supplementary table 1) of clearly stated polyp adjacent biopsies was consistent with the data presented herein.

In conclusion in our centre over recent a five-year period the diagnostic yield for polyp adjacent biopsies in patients with IBD was found to be negligible. We suggest that with contemporary use of high definition technology and chromoendoscopy it may no longer be necessary to biopsy endoscopically normal adjacent tissue to detect invisible dysplasia.

Conflicts of Interest

CL: None

LMW: LMW to include

SPLT: ST to include

JEE: Lumendi, Olympus, Cosmo Pharmaceuticals

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References

Figure Legends

Figure 1.

Study flow diagram illustrating methodology for original data search, including search terms (n=602). After exclusions and collecting data from endoscopy, histology and electronic patient records, per patient (n=138) and per polyp (n=302) data analyses were carried out separately.

Figure 2.

Polyp type distribution for all polyps (n=302). Neoplastic and non-neoplastic findings are grouped separately.

Figure 3.

Images A and B show high-definition white light and chromoendoscopy images of a circumferential laterally spreading tumour in the transverse colon of a patient with pan-ulcerative colitis. This patient was found to have multifocal dysplasia and was recommended to have a colectomy. Image C shows a suspicious depressed rectal mass lesion which was subsequently found to be cancer (pT2, N0, M0; alive without disease January 2017).

Tables

Patients	n=131
Age (median, range)	60 (17-82)
Gender (male/female, %)	75/56 (57)
Disease duration* (median, range)	20 (1-58)
Ulcerative colitis (%)	123 (94)
- E1 / E2 / E3	5 / 35 / 82
- Not available	1
Crohn's colitis (%)	6 (5)
IBD unclassified (%)	2 (1)
Concomitant PSC (%)	30 (23)
No. procedures per patient (%)	
1	98 (75)
2	22 (17)
3	8 (6)
4	3 (2)
No. polyps per patient (%)	
1-2	100 (76)
3-4	15 (11)
>4	16 (12)

Table 1. Patient demographics and disease related variables for all 131 patients. *Disease duration was available for 116 patients (89%).

Total polyps	n=302
Polyp size* (mm)	
- Median	4
- Range	1-45
Adjacent biopsy (%)	
- Stated	68 (23)
- Segmental	161 (53)
- None	73 (24)
Dysplasia in polyp (%)	
- Low grade	89 (29)
- High grade / cancer	6 (2)
- None	205 (68)
- Not available	2 (1)
Dysplasia in adjacent biopsy (%)	
- Yes	2 (1)
- No	230 (76)
- Not available	70 (23)
Polyp size >10mm (%)	32 (11)
- Low grade	9 (28)
- High grade / cancer	2 (6)
- SSP/L	8 (25)
- Other	13 (41)
Adjacent biopsies (>10mm, %)	
- Stated	11 (34)
- Segment	9 (28)
- None	12 (38)

Table 2. All polyps resected or biopsied (n=302). *Polyp size was recorded in 139 (46%). Adjacent biopsies were defined as either stated (free text) on the endoscopy report, taken from the same colonic segment as the polyp or not taken. Two polyps (1%) were not retrieved and therefore dysplasia in these polyps was not available.

Total cases dysplasia = 71	Dysplasia (%)	Adjacent biopsies (%)	P value	Adjacent dysplasia (%)	P value
Centre					
- Tertiary	54 (76)	46 (85)	0.72	2 (3)	0.99
- District	17 (24)	14 (82)		0 (0)	
Endoscopist					
- IBD/Endo.	23 (32)	21 (91)	0.48	1 (4)	0.55
- Other	48 (68)	39 (81)		1 (2)	
Chromoendoscopy	16 (23)	15 (94)	0.44	1 (6)	0.40
WLE	55 (77)	45 (82)		1 (2)	
HD	17 (24)	13 (76)	0.44	1 (6)	0.44
Standard	54 (76)	47 (87)		1 (2)	

Table 3. Sensitivity analysis for procedural and operator related factors in cases of dysplastic polyps (n=71) which may have influenced either likelihood for adjacent biopsies to be taken, or to yield dysplasia. Analyses are presented for tertiary vs. district general hospitals, IBD specialist vs. non-specialist endoscopists, chromoendoscopy vs. white light and high definition vs. standard definition endoscopes.

Figures

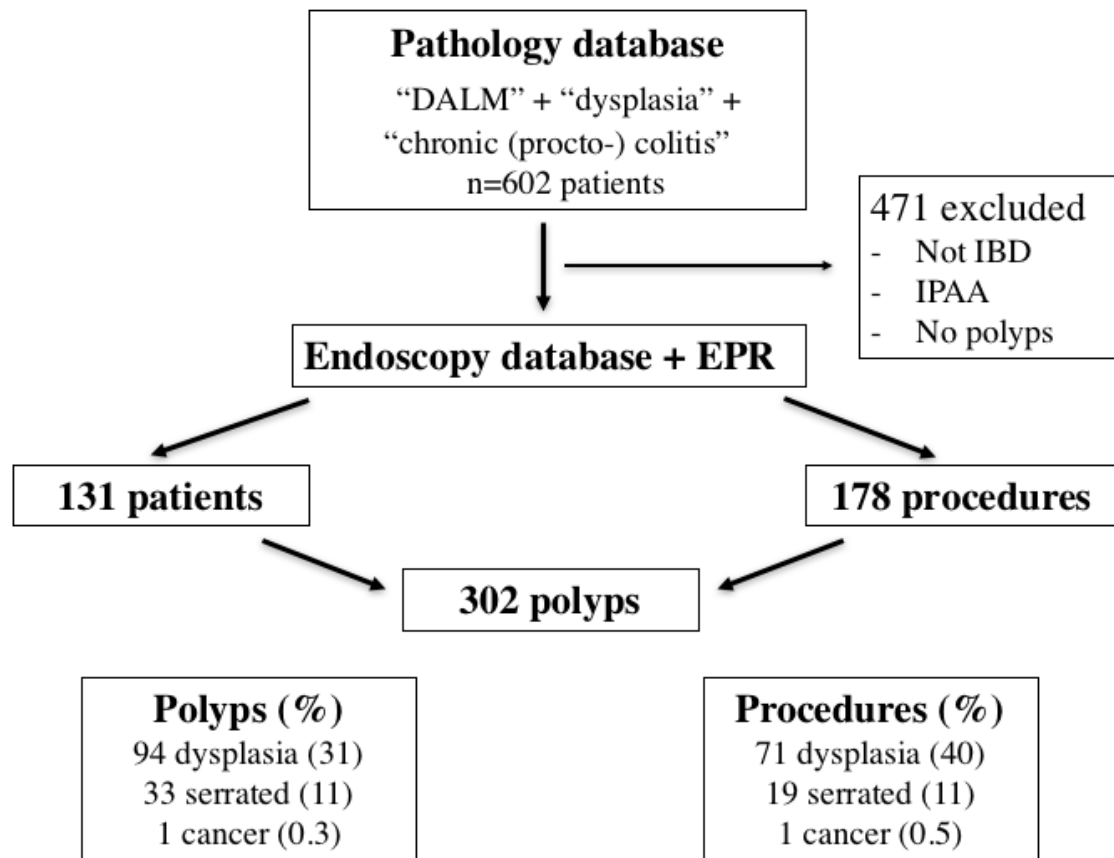


Figure 1

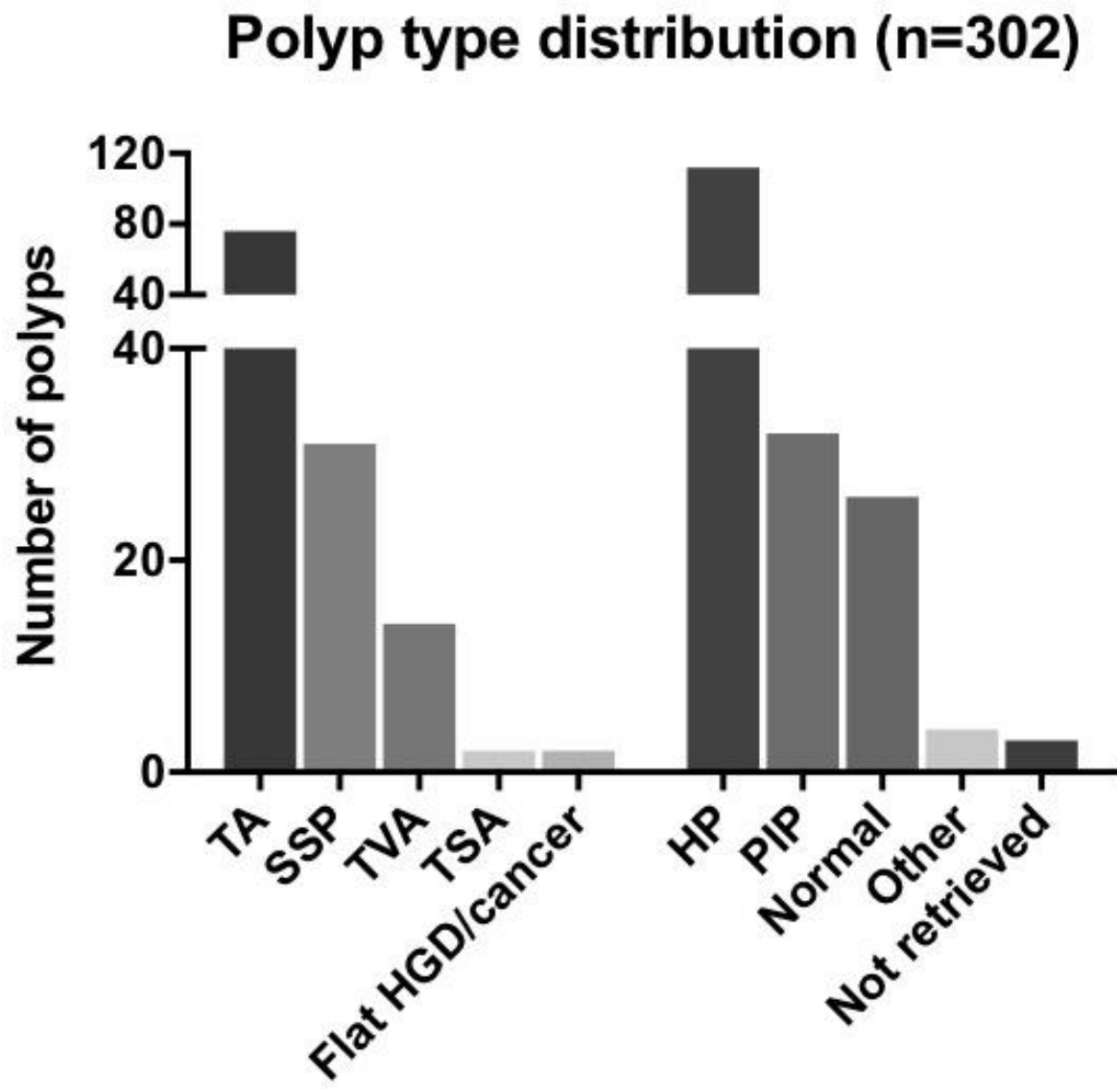


Figure 2

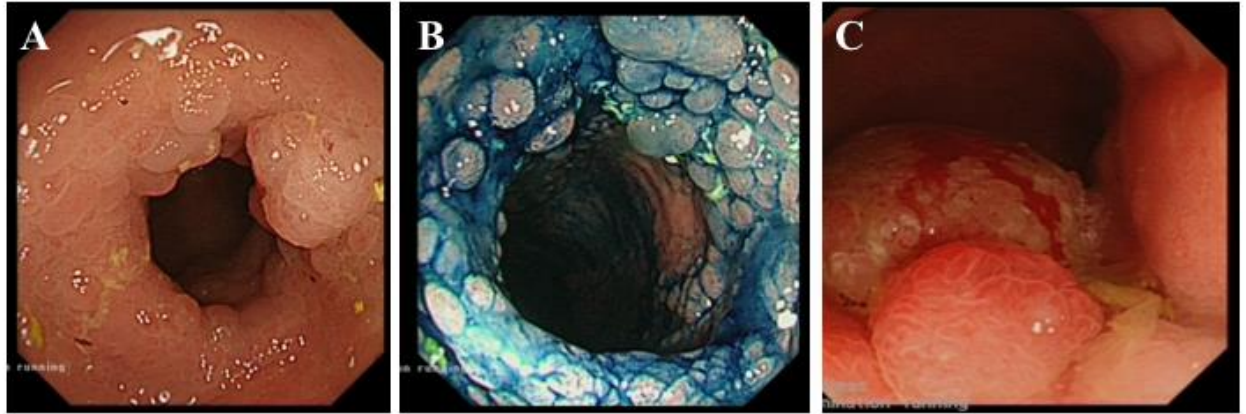


Figure 3

Total polyps with stated adjacent biopsies	n=68
Polyp size* (mm)	
- Median	4
- Range	1-40
Dysplasia in polyp (%)	
- Low grade	17 (25)
- High grade / cancer	2 (3)
- None	48 (71)
- Not available	1 (1)
Dysplasia in adjacent biopsy (%)	
- Yes	1 (1)
- No	67 (99)
Polyp size >10mm (%)	11 (16)
- Low grade	2 (18)
- High grade / cancer	1 (9)
- SSP/L	5 (45)
- Other	3 (27)

Supplementary table 1. All polyps resected or biopsied with stated adjacent biopsies (n=68). *Polyp size was recorded in 46 (68%). One polyp (1%) was not retrieved.