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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 adjacent mucosa to determine whether there is dysplasia present. With improvements in endoscopic imaging, it is now possible to characterize colonic lesions with higher levels of confidence than previously. We have reviewed the diagnostic yield of polyp-adjacent biopsies in IBD.

Materials and Methods: A systematic search of our histopathology database revealed cases in which 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. The median polyp size was 4 mm (range 1–45), and the predominant morphology was Paris 0–Is ($n = 98$, 32%). The 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.

Key Words: IBD; polyp; dysplasia; high-definition; chromoendoscopy

Abbreviations: ALM, adenoma-like mass, DALM, dysplasia-associated lesion or mass, LGD, low-grade dysplasia, HGD, high-grade dysplasia, CRC, colorectal cancer, SCENIC, Surveillance for Colorectal Endoscopic Neoplasia Detection and Management in Inflammatory Bowel Disease Patients: International Consensus Recommendations

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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[1–3] to have biopsies taken from the area immediately adjacent to the resected polyp. The aim of these adjacent biopsies is to detect endoscopically invisible dysplasia. This recommendation is not strongly evidence based. Although histopathology guidelines[4] support this practice, no guideline describes a clear protocol, and there is no recommendation about the number of biopsies or the distance from the resected lesion. The concept of taking polyp-adjacent biopsies arose from the dated concept of distinguishing an adenoma-like mass (ALM) from a dysplasia-associated lesion or mass (DALM). This terminology has been discouraged by contemporary guidelines[3] in favour of a shift towards the more helpful distinction between visible, circumscribed dysplasia and endoscopically invisible dysplasia, previously described as 'flat' dysplasia.

It is now apparent that the risk of advanced neoplasia and colorectal cancer (CRC) in patients with colitis has been overstated[5,6], with population-based estimates showing lower risk.[7–9] While large-cohort studies have shown increased dysplasia detection over recent years,[10] colitis-associated CRC rates appear to be decreasing in patients undergoing surveillance.[7,10] Whether this is due to improved medical therapy with a reduced cumulative inflammatory burden 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 remains poorly understood, but it appears that carefully resected sporadic lesions, particularly those of smaller (<10 mm) size and sessile or pedunculated (Paris 0–I) appearance, may not carry a significantly heightened long-term CRC risk.[11–14] Other risk factors clearly need to be considered when deciding upon subsequent surveillance intervals, such as historical inflammatory burden, presence of multiple post-inflammatory polyps (perhaps a surrogate for inflammatory burden), primary sclerosing cholangitis (which may often be undetected[15]), or family history of CRC.[16]

Studies examining the diagnostic value of polyp-adjacent mucosal biopsies are few. A recent study from the Netherlands,[17] however, supports a low diagnostic yield and 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 technique, technology, poor endoscopic views and physician concerns in relation to missed lesions.[18] Endoscopists have therefore relied upon histopathology as a gold-standard technique for dysplasia detection. The conventional recommendation in the absence of advanced endoscopic techniques has been for random quadrantic biopsies every 10 cm when performing surveillance in patients with colitis.[2] Pan-colonic dye spray (chromoendoscopy), with or without high-definition imaging, is now recommended as the gold-standard technique for surveillance in IBD[1,3] since this is associated with enhanced neoplasia detection. Nevertheless, it appears that even with standard-definition modern video endoscopes, most dysplasia is endoscopically visible.[19,20] The SCENIC consensus further proposed that with appropriate training and use of advanced techniques, circumscribed lesions could accurately be characterized with a high level of confidence and resected safely, followed by close endoscopic surveillance. Risk of cancer progression for colitis-associated lesions is ~14 cases per 1000 years of patient follow-up.[6] The risks associated with resected polypoid dysplastic lesions are considerably lower.[14] Evidence suggests that such lesions can be safely managed by standard polypectomy and surveillance.[3,12–14] With a move away from random biopsies to a targeted approach now adopted in the context of surveillance, our hypothesis 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 at a university hospital. Patients with IBD predominantly came from their local population and allied district general hospital (80%), as well as tertiary referrals to an academic hospital with subspecialty interests in IBD and therapeutic endoscopy (20%). Ethical approval for the study was granted by the Trust Research Ethics Committee as a clinical practice audit (clinical audit #4314).

A systematic search of the hospital histopathology database, using search terms 'dysplasia', 'DALM', 'chronic colitis' and 'chronic proctocolitis' for the period January 2010 to December 2015 identified cases in which 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). For external validation, the final study cohort was cross-referenced against patients screened for a prospective IBD surveillance clinical trial (CPMS ID 15360). 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.

The categories used were 'negative for dysplasia', 'indefinite for dysplasia', 'low-grade dysplasia', 'high-grade dysplasia' and 'adenocarcinoma (defined by submucosal invasion)' as per UK guidelines for reporting colorectal neoplasia, allowing comparison with the USA and European literature. Dysplastic and indefinite-for-dysplastic lesions were reported by two GI pathologists, and challenging cases had additional p53, beta-catenin and Ki67 immunohistochemical studies performed as an adjunct to diagnosis.

Search methods and numbers of exclusions are further detailed in Figure 1. Descriptive statistics used Vassar Stats (www.vassarstats.net). Sensitivity analyses were performed to assess the impact of procedural and operator-related variables on the diagnostic yield from polyp-adjacent biopsies. The study is reported according to the STROBE guidelines.[21]

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 shown in Table 1. The median patient age was 60 (range 17–82), with 43% female. One hundred and twenty-three patients (92%) had ulcerative colitis, most with pancolitis (E3). Six patients had Crohn's colitis and 2 IBD–unclassified. Thirty patients (23%) had primary sclerosing cholangitis (PSC). The median disease duration was 20 years (range 1–58 years). Most patients (52%) were on 5-aminosalicylic acid (5-ASA)-based

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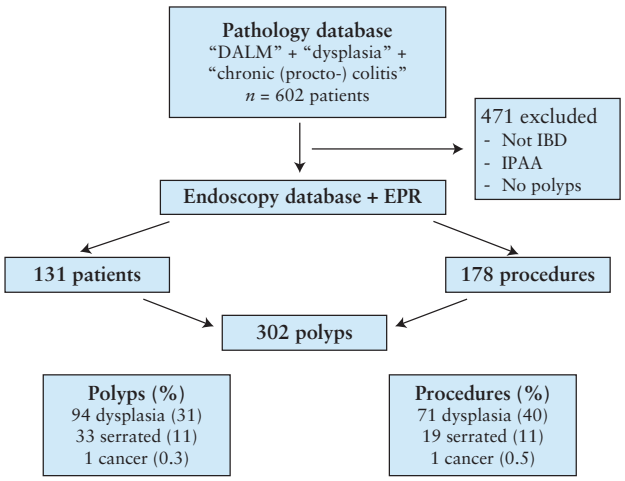

Figure 1. Study flow diagram illustrating methodology for original data search, including search terms (n = 602). After exclusions and collecting data from endoscopy, histology and electronic patient records, per patient (n = 138) and per polyp (n = 302) data analyses were carried out separately.

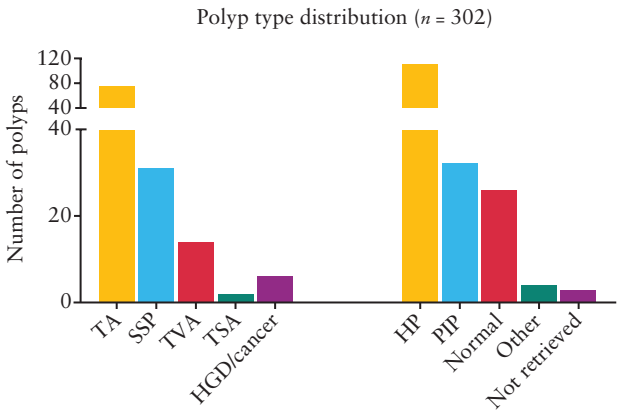

Figure 2. Polyp type distribution for all polyps (n = 302). Neoplastic and non-neoplastic findings are grouped separately. TA = tubular adenoma, SSP = sessile serrated polyp, TVA = tubulovillous adenoma, TSA = traditional serrated adenoma, HGD = high-grade dysplasia, HP = hyperplastic, PIP = post-inflammatory polyp. Other (n = 4) includes lymphoid tissue (n = 1), lipoma (n = 2) and prolapse (n = 1).

Table 1. Patient demographics and disease-related variables for all 131 patients.

Patients	n = 131
Age (median, range)	60 (17–82)
Gender (male/female, %)	75/56 (57)
Disease duration[a] (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)

[a]Disease duration was available for 116 patients (89%)

Table 2. All polyps resected or biopsied (n = 302).

Total polyps	n = 302
Polyp size[a] (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 >10 mm (%)	
– Low grade	32 (11)
– High grade / cancer	9 (28)
– SSP/L	2 (6)
– Other	8 (25)
Adjacent biopsies (>10 mm, %)	13 (41)
– Stated	11 (34)
– Segment	9 (28)
– None	12 (38)

[a]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.

monotherapy (full medication details are included in Supplementary Table 1).

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%), high-grade dysplasia or cancer in 6 (2%) and normal (n = 26), not retrieved (n = 3) or other (n = 4, see Figure 2 legend) in 33 (11%).

The median polyp size (Table 2) was 4 mm (range 1–45). The degree of dysplasia in polyps was low grade in 89 patients (29%) and 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 proximal to the splenic flexure in 162 (54%).

Adjacent biopsies were those 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

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(Figure 3). The proportion of endoscopically unsuspected dysplasia revealed by adjacent biopsies was 0/300 (0%, 95% CI 0–1.6%).

Sensitivity analyses were carried out for the procedures where dysplasia was detected (n = 71, Table 3), and for all dysplastic polyps (n = 94, Table 4) for factors which may have influenced either the likelihood for adjacent biopsies to be taken, or for those biopsies to have yielded dysplasia. Operator- and procedure-related characteristics were assessed for parent Teaching vs allied District General Hospitals, IBD specialist vs non-IBD specialist endoscopist, procedure indication (surveillance vs disease assessment), chromoendoscopy vs white light and high-definition vs standard-definition endoscopes, which did not show any differences in outcomes. Patient-specific

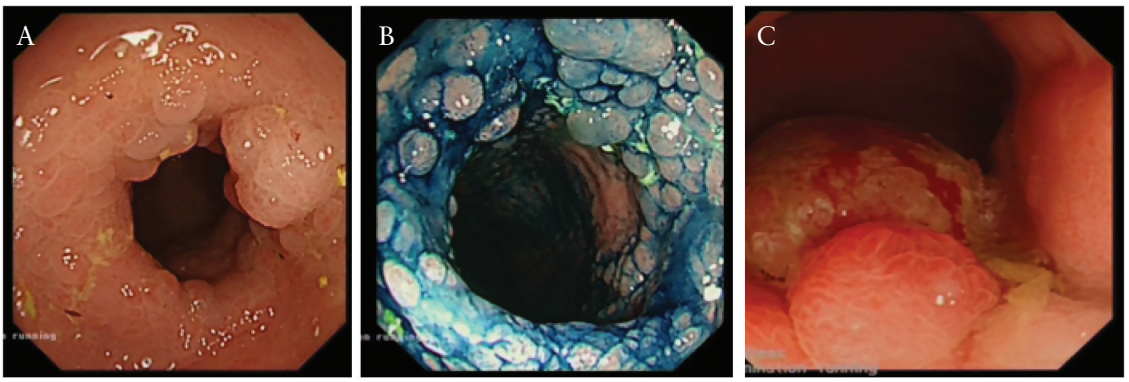

Figure 3. Images A and B show high-definition white light and chromoendoscopy images of a circumferential laterally spreading tumour in the transverse colon of a patient with pan-ulcerative colitis. This patient was found to have multifocal dysplasia and was recommended to have a colectomy. Image C shows a suspicious depressed rectal mass lesion that was subsequently found to be cancer (pT2, N0, M0; alive without disease January 2017).

Table 3. Sensitivity analysis for procedural- and operator-related factors in cases of dysplastic polyps (n = 71) that 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, procedure indication, chromoendoscopy vs white light and high-definition vs standard-definition endoscopes.

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			0.48		0.55
— IBD/Endo.	23 (32)	21 (91)		1 (4)	
— Other	48 (68)	39 (81)		1 (2)	
Procedure indication			0.49		0.42
— Surveillance	54 (76)	45 (83)		1 (2)	
— Assessment	17 (24)	13 (76)		1 (6)	
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 4. Sensitivity analysis for potential factors that may have been expected to influence endoscopists' assessment of neoplasia-related risk for each dysplastic polyp (n = 94) and thus may have influenced the likelihood for adjacent biopsies to be taken. A further sensitivity analysis was carried out to determine any impact on dysplasia yield for adjacent biopsies. Analyses are presented for polyp location, size and total number per procedure.

Total polyps dysplasia = 94	Dysplasia (%)	Adjacent biopsies (%)	p value	Adjacent dysplasia (%)	p value
Location					
Post-colitic	72 (77)	54 (75)	0.58	2 (3)	0.99
Non-colitic	22 (23)	15 (68)		0 (0)	
Size (mm)			0.99		0.06
<10	33 (75)	24 (73)		0 (0)	
≥10	11 (25)	8 (73)		2 (18)	
Number			0.99		0.22
1–2	83 (88)	61 (73)		1 (1)	
≥3	11 (12)	8 (73)		1 (9)	

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endoscopic factors that may have been expected to confer higher risk of advanced neoplasia were further analysed to determine effect on likelihood of polyp-adjacent biopsies being taken or likelihood of detecting dysplasia in those biopsies. No significant relationships were observed for these factors (Table 4).

The median duration of follow-up was 29 months (range 0–79). During our period of follow-up, 6 patients underwent colectomy, including 2 for CRC, 1 for HGD (CRC in colectomy specimen), 2 for multifocal LGD and 1 for medically refractory colitis. In the 2 patients where polyp-adjacent dysplasia was found (Figure 3), colectomy was recommended and 1 (C, Figure 3) had cancer.

A time trend analysis (Figure 4) shows the increased use of chromoendoscopy and high-definition colonoscopes during the period of study and contrasts with the rate of polyp-adjacent biopsy. The non-biopsy rate increases gradually during the early period (10% in 2010 to 40% in 2013), in conjunction with increased utilization of advanced techniques, but then falls again in the later period, to 10% in 2015. The dysplasia rate per polyp follows a similar trend, peaking at 60% in 2011 and then falling to 27% in 2015.

Discussion

Our data suggest that the diagnostic yield for polyp-adjacent biopsies in IBD is negligible. The yield for unexpected, 'invisible' dysplasia was zero in our cohort, since both lesions for which dysplasia was detected in adjacent biopsies had endoscopically suspicious appearances. Other data, although limited to a single study, support a similar conclusion and further suggest that there is no clinical value in carrying out routine polyp-adjacent biopsies.[17] This Dutch study was carried out in referral centres and focused on patients participating in a surveillance programme. Our study relates primarily to secondary care, with only 20% tertiary referrals, and also includes a spectrum of endoscopic training and expertise. It appears from our analysis that higher-level advanced endoscopic techniques or equipment, although expected to be helpful in aiding assessment and resection of lesions, are not essential to a good outcome. Even with standard-definition endoscopes and more general gastroenterology practice, polyp-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.[22] In keeping with SCENIC recommendations,[3] we agree that where the extent or resectability of a lesion is unclear, referral to a specialist IBD endoscopist should be standard practice.

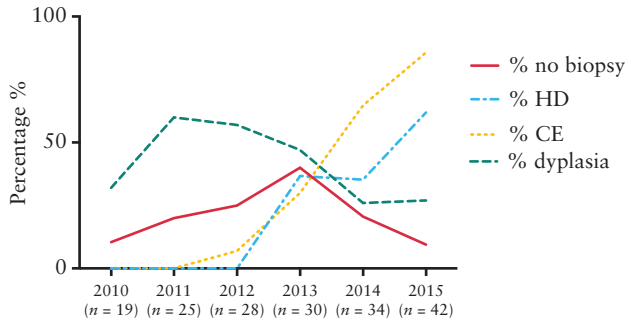

Figure 4. Time trend analysis for rate of absence of polyp-adjacent biopsy for all procedures over the period of study. Non-biopsy rate (solid line) is compared with increased use of chromoendoscopy and high-definition endoscopes for procedures. Dysplasia rate per polyp is also presented. HD = high definition, CE = chromoendoscopy.

The concept of field cancerization suggests that molecular or epigenetic changes might occur throughout the intestinal epithelium in patients with IBD. This could significantly increase the risk of CRC developing.[23,24] Such molecular changes can occur early and have been shown to pre-date the development of dysplasia. It is therefore possible that owing to sampling error or other factors, negative adjacent biopsies might provide a false sense of security in the stratification of future neoplastic risk for individual patients. It may be that molecular changes are a better marker of risk for IBD-associated cancer. The development and validation of reproducible assays that allow better risk stratification for patients undergoing surveillance remains essential for determining personalized management strategies.

Our sensitivity analysis suggests that procedural and patient- or polyp-specific factors do not have any influence on the likelihood for polyp-adjacent biopsies to be taken or on the likelihood for these biopsies to yield dysplasia. There was a trend toward larger lesions (>10 mm) perhaps showing a propensity toward higher risk for adjacent dysplasia. This was also suggested by Ten Hove et al.[17] However, the incident rate for polyp-adjacent dysplasia in our study (n = 2) was too small to allow any firm conclusions to be reached, and importantly these lesions were endoscopically visible and therefore dysplasia was not unexpected.

While the distinction between sporadic and colitis-associated lesions can be useful and inform decision-making regarding surveillance intervals, it should be possible to determine sporadic from colitis-associated lesions from endoscopic appearances and clinical history in most cases. Histology can provide further information and guide decision-making where there is uncertainty. In this instance, non-lesional biopsies can be valuable for determining the extent of disease and degree of inflammation.

The time trend analysis of the non-biopsy rate highlights the strikingly low rate of compliance with a multiple society guideline recommendation. This may imply a shift in practice over time, in which endoscopists, becoming increasingly confident in their ability to distinguish significant lesions are electing to rely more heavily on their endoscopic impression. A similar trend is also noted in the Ten Hove paper.[17] The dysplasia rate per polyp in this same analysis rises in conjunction with the rising non-biopsy rate, and these two trends together may reflect the learning curve in chromoendoscopy.[25] Reasons for the attenuation in both graphs in the latter years of study are unclear and difficult to ascertain from the present study design.

Our study has some strengths, including a heterogeneous cohort of patients with IBD closely followed over a long period of time (median 29 months). It also has some limitations. These include the retrospective nature of the study and the possibility that database search criteria could have missed relevant patients, and the rate of non-biopsy adjacent to resected polyps. The rate of non-biopsy was consistent with other data[17] and probably implies a shift in practice to physicians who already exclude unsuspicious lesions from adjacent biopsies. Only a longitudinal, registry outcome study or prospective randomized trial will answer the question about the value of polyp-adjacent biopsies. Our endoscopy-reporting system does not have a designated field for adjacent biopsies, so our approach of including those with polyp-adjacent biopsies from free text and biopsies from the same segment as the polyp may have overestimated the denominator. When we analysed only those patients with clearly stated polyp-adjacent biopsies, our results were consistent with the overall analysis (Supplementary Table 2). The relatively

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higher proportion of UC over Crohn's patients is reflective of overall risk of developing neoplasia as well as real-life surveillance practices in our centre. The proportion of PSC patients in our cohort is also high (23%); it is more frequently associated with UC than Crohn's colitis, and that may further explain the observed UC predominance. While endoscopic appearances may differ between UC and Crohn's, and this may present challenges in lesion characterization, the same principles should apply in terms of polyp-adjacent biopsies for Crohn's disease, and this is supported by other studies.[17]

Over a 6-year period, the diagnostic yield for adjacent biopsies from 302 polyps in 131 patients with IBD was found to be negligible. Contemporary endoscopic technology means that it may no longer be necessary to biopsy apparently normal polyp-adjacent tissue to detect invisible dysplasia.

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Conflict of Interest

CL: None declared.
LMW: None declared.
SPLT: Simon Travis has been an adviser to, received educational or research grants from, or been an invited lecturer for AbbVie, Amgen, Asahi, Biogen, Boehringer Ingelheim, BMS, Cosmo Pharmaceuticals, Elan, Enterome, Ferring, FPRT Bio, Genentech/Roche, Genzyme, Glenmark, GW Pharmaceuticals, Johnson & Johnson, Lilly, Merck, Novartis, Novo Nordisk, Ocera, Pfizer, Santarus, Shire, SigmoidPharma, Synthon, Takeda, Tillotts, Topivert, Trino Therapeutics with Wellcome Trust, UCB Pharma, Vertex, VHsquared, Vifor, Warner Chilcott, and Zeria. All advisory boards were suspended while President of ECCO.
JEE: Lumendi, Olympus, Cosmo Pharmaceuticals.

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Author Contributions

CL was involved in the conception and design of the study, acquisition of data, analysis and interpretation of data, drafting the article and final approval of the version to be submitted.
LMW was involved in the conception and design of the study, acquisition of data, revising the article critically for important intellectual content and final approval of the version to be submitted.
SPLT was involved in the conception and design of the study, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be submitted.
JEE was involved in the conception and design of the study, analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be submitted.

Supplementary Data

Supplementary data for this article can be found at *Journal of Crohn's and Colitis* online.

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