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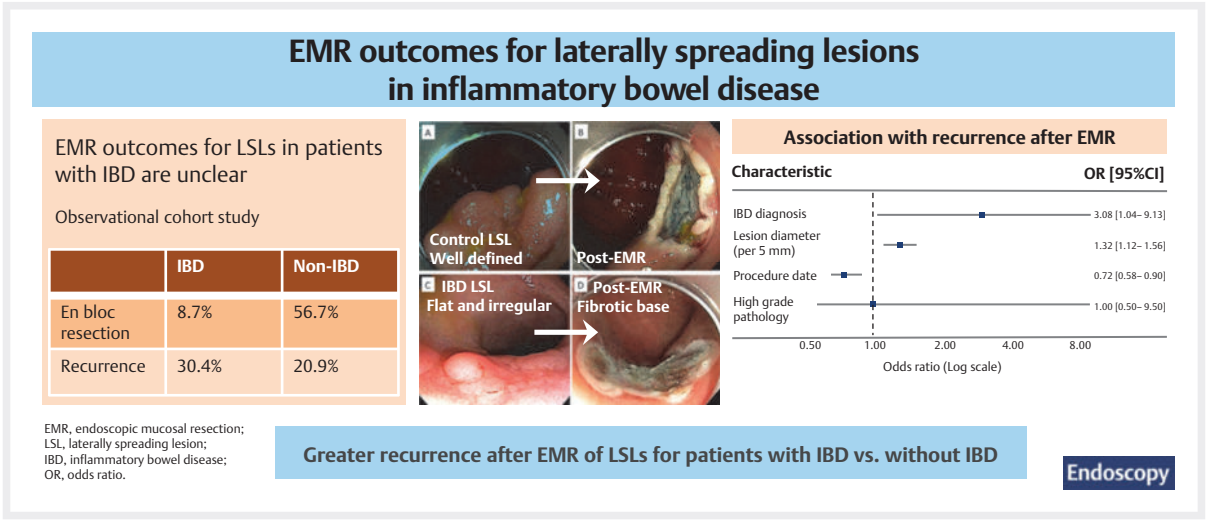
Comparative outcomes of endoscopic mucosal resection for laterally spreading lesions in inflammatory bowel disease

GRAPHICAL ABSTRACT



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received 27.10.2023
accepted after revision 19.7.2024
accepted manuscript online 19.7.2024
published online 2024

Bibliography
Endoscopy
DOI 10.1055/a-2369-7980
ISSN 0013-726X

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Supplementary Material
Supplementary Material is available at https://doi.org/10.1055/a-2369-7980

ABSTRACT

Background The role of endoscopic mucosal resection (EMR) for laterally spreading lesions (LSLs) in inflammatory bowel disease (IBD) remains controversial despite its effectiveness in the general population. We aimed to characterize outcomes of EMR for IBD-associated LSLs compared with controls without IBD.

Methods We performed a retrospective observational cohort study of patients with IBD who underwent EMR and endoscopic follow-up for LSLs, compared with a control group without IBD. The primary outcome was histologic recurrence. Secondary outcomes included en bloc resection and adverse events. Factors associated with recurrence were identified using multivariate mixed effects logistic regression.

Results 210 premalignant lesions in 155 patients were included. By histology, 91.0% were adenoma/low grade dysplasia or sessile serrated lesions. Median (IQR) lesion size was 25 (12–30) mm in the IBD group and 20 (12–30) mm

in the control group. Recurrence was detected in 30.4% of IBD-associated lesions (7/23) compared with 20.9% of controls (39/187; odds ratio [OR] 2.51, 95%CI 0.59–10.71). En bloc resection was less common in the IBD group (2/23 [8.7%], 95%CI 1.1–28.0) versus controls (106/187 [56.7%], 95%CI 50.4–65.2). After adjusting for lesion size and histology, recurrence appeared more common in patients with IBD compared with controls (OR 3.08, 95%CI 1.04–9.13).

Conclusions Recurrence of LSLs after EMR appeared to be more frequent in patients with IBD. Given the added complexity, EMR in patients with IBD should be performed in expert centers with close endoscopic surveillance.

Introduction

The incidence rate of colorectal cancer in inflammatory bowel disease (IBD) is estimated to be 75.0–76.0 per 100 000 person-years compared with 47.1 per 100 000 person-years in those without IBD [1, 2]. This risk is increased by duration of disease as well as patient-specific factors including disease extent and activity, family history of colorectal cancer, personal history of dysplasia, and high risk endoscopic features [3]. Intestinal inflammation is known to be an independent driver of oncogenesis and may have important implications in IBD-associated tumor initiation, growth, and invasion [4].

Surveillance colonoscopy may be beneficial for early identification of premalignant lesions in this group, and previously the detection of flat dysplastic lesions has prompted colectomy [5]. The landscape of dysplasia surveillance in IBD has undergone a transformational change over the past decade, with improvements in optical imaging techniques (i. e. chromoendoscopy, narrow-band imaging, and high definition white-light endoscopy) enabling reliable detection of nonpolypoid dysplasia [6]. Endoscopic mucosal resection (EMR) has emerged as a powerful technique for nonpolypoid laterally spreading lesions (LSLs) in the general population [7]. The landmark 2015 SCENIC guidelines recommended the use of enhanced imaging techniques for evaluation of nonpolypoid dysplasia in IBD and removal by endoscopic means if the lesions were clearly delineated [5]. Experience in performing EMR has increased in tandem with advancements in endoscopic resection devices and techniques, which have in turn impacted recent guidelines, suggesting that endoscopic resection is attempted for all clearly defined LSLs before considering surgery in patients with IBD.

Nevertheless, LSLs frequently require advanced endoscopic resection due to large size and complex morphology. Additionally, inflammation- and fibrosis-driven changes in colitis may increase the difficulty of EMR through a variety of mechanisms including failure of lifting and distortion of mucosal pit patterns [8].

Our aim was to characterize the outcomes of endoscopic resection of IBD-associated LSLs compared with controls without IBD but with similar size and morphology in a real-world population.

Methods

Study design

We performed a retrospective observational cohort study at the Keck Medical Center of the University of Southern California, a large academic tertiary referral center. We identified all premalignant LSLs removed with EMR from 31 December 2015 to 31 December 2021 that subsequently underwent at least one session of endoscopic surveillance by colonoscopy. LSLs with malignant potential included histologically confirmed adenomas, sessile serrated lesions, and those with features of high grade dysplasia or carcinoma. Lesions without significant malignant potential upon histologic examination, such as hyperplastic and inflammatory lesions, were excluded. Lesions resected using procedures other than EMR, such as endoscopic submucosal dissection (ESD) or full-thickness endoscopic resection, were also excluded from the study.

All procedures were performed by gastrointestinal attending endoscopists, all of whom had performed at least 1000 colonoscopies and 50 EMR procedures. While the great majority were performed by advanced endoscopists with dedicated training in mucosal resection and extensive experience, we also included EMR performed by IBD specialists with less experience in resection to reflect real-world practice.

CPT code 45390 was used to identify colonoscopies with EMR. ICD-10 codes K50–52 were used to identify patients with Crohn's disease or ulcerative colitis.

Prior to initiation of study activities, the study was approved by the University of Southern California institutional review board (registration number HS-21–00736).

Data collection

Patient-level characteristics at the time of the index procedure included presence of IBD (Crohn's disease or ulcerative colitis), age, sex, self-reported race/ethnicity, body mass index, and number of lesions. Ongoing systemic steroids or biologic use was recorded. Lesion-level characteristics collected at the index procedure included need for surgical resection as definitive treatment, location within the colon, margins (en bloc vs. piecemeal), morphology (flat, sessile, pedunculated), premalignant potential upon histopathologic analysis (sessile serrated lesion or low grade dysplasia, high grade dysplasia, invasive carcinoma), lesion size, and duration of the procedure.

Post-resection surveillance endoscopy reports were reviewed for each index lesion. Data from biopsies taken during follow-up surveillance procedures were collected to determine histologic recurrence.

Adverse events were categorized as bleeding, perforation, post-polypectomy syndrome, or admission >1 day.

EMR procedures

EMR procedures were routinely performed with submucosal injection of saline with or without methylene blue dye or with a commercially available lifting agent, such as Eleview submucosal injectate (Medtronic, Minneapolis, Minnesota, USA). Resection was usually performed using a 15–25-mm snare with electrocautery. Patients undergoing underwater EMR without submucosal injection were also included. Cold snare EMR and underwater EMR were used in a minority of cases. At our center, a pediatric colonoscope (CF-190, PCF-190; Olympus, Tokyo, Japan) with or without an attached transparent hood was used for resection using an electrosurgical unit (VIO300 D or VIO3; Erbe, Tübingen, Germany), under a carbon dioxide insufflation system (ECO2; Erbe). Closure of the mucosal defect with endoscopic clips was routinely performed in the majority of cases. EMR was not performed in areas of active inflammation. If a polyp that required EMR was found in the presence of active inflammation, it is the practice at our institution to medically treat the patient for 3 months and proceed with EMR after confirmation that endoscopically visible inflammatory changes have resolved.

Outcome measurement

The primary outcome was histologically confirmed recurrence of premalignant lesions for IBD- vs. non-IBD-associated lesions. Biopsy samples were taken at EMR sites during follow-up endoscopies for post-resection surveillance. The initial surveillance exam was typically performed within 3–6 months after resection. Secondary outcomes were successful en bloc removal vs. piecemeal resection, procedure time, post-procedural adverse events, and the need for surgical intervention for definitive treatment. En bloc resection was defined as resection that was completed in one piece as determined by the endoscopist. Outcomes are reported on a per-lesion basis except for procedure time, which is defined as the time elapsed from entry of the endoscope into the colon to removal. Baseline features are reported both on a per-patient and per-lesion basis.

Statistical analysis

Patient- and lesion-level characteristics are described using frequencies (percentages) and medians (interquartile range [IQR]) depending on the distribution. Patient-level characteristics were compared using chi-squared, Fisher's exact, and Wilcoxon rank sum tests, as appropriate. Lesion-level characteristics were compared using a logit model (IBD as the dependent variable) with cluster-robust standard errors to account for within patient correlation.

Mixed effects logistic regression was used to estimate univariate odds ratios (OR) with 95%CI for recurrence while accounting for within-patient correlation in the presence of multiple LSLs per patient. Factors evaluated for association with recurrence included the primary exposure of interest (IBD), characteristics with differing distributions by IBD (age and year of procedure), and lesion characteristics potentially impacting recurrence (size and degree of dysplasia). The final multivariate analysis was adjusted for clinically and statistically relevant (univariate $P<0.2$ using backward elimination; $P>0.05$ for removal) factors with degree of dysplasia retained due to strong a priori biological association with recurrence mandating inclusion. In an exploratory analysis, we further adjusted for procedural factors of potential interest to endoscopists, including the use of specific lifting agents and thermal margin ablation.

Statistical significance was defined as <0.05. As this study explores a single primary outcome, there was no adjustment for multiple testing. Additional analyses were exploratory or for secondary outcomes. Statistical analyses were completed in SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) or Stata MP 17.0 (StataCorp LLC, College Station, Texas, USA).

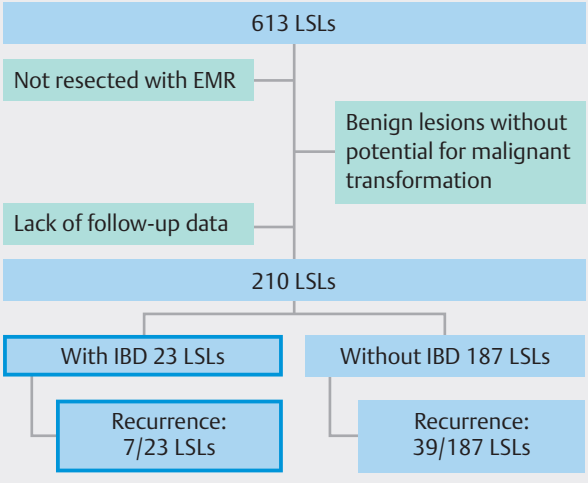
Results

Patient and lesion characteristics

A total of 210 premalignant lesions in 155 patients were included. Overall, 50.6% of patients were female (▶ **Table 1**). There were 23 lesions in 14 patients with IBD and 187 lesions in 141 patients without IBD (▶ **Fig. 1**). Among the group of patients with IBD, 7 had ulcerative colitis and 7 had Crohn's disease. Full demographic data are presented in ▶ **Table 1**.

Most of the lesions were located in the right colon: 35.8% of lesions were found in the ascending colon, 22.8% in the transverse colon, and 15.0% in the cecum (▶ **Table 2**). All patients had quiescent IBD at the time of EMR. We confirmed that 19/23 lesions were at sites of prior documented inflammation. While records of prior colonoscopy were not available for the other four patients, they were known to have a history of pancolitis.

The median (IQR) lesion size was 20 (12–30) mm overall, 25 (12–30) mm in the IBD group, and 20 (12–30) mm in the control group. Morphology upon endoscopic visualization was described as sessile for 52.9% of lesions (IBD 57.1%, non-IBD 52.5%) and flat for 47.1% of lesions (IBD 42.9%, non-IBD



▶ **Fig. 1** Study selection flow diagram. EMR, endoscopic mucosal resection; IBD, inflammatory bowel disease; LSL, laterally spreading lesion.

▶ **Table 1** Patient-level characteristics for those with and without inflammatory bowel disease who underwent colorectal endoscopic mucosal resection for premalignant laterally spreading lesions.

	Control N = 141 (91.0%)	IBD N = 14 (9.0%)	*P* value
Sex,[1] n (%)			0.54
▪ Female	72 (51.4)	6 (42.9)	
▪ Male	68 (48.6)	8 (57.1)	
Ethnicity,[2] n (%)			0.83
▪ White	83 (59.7)	9 (64.3)	
▪ Hispanic	25 (18.0)	3 (21.4)	
▪ Other	13 (9.4)	2 (14.3)	
▪ Asian	12 (8.6)	0 (0.0)	
▪ Black	6 (4.3)	0 (0.0)	
Multiple polyps, n (%)	33 (23.4)	5 (35.7)	0.33
Number of polyps, n (%)			0.50
▪ 1	108 (76.6)	9 (64.3)	
▪ 2	18 (12.8)	3 (21.4)	
▪ 3	8 (5.7)	1 (7.1)	
▪ ≥4	7 (4.9)	1 (7.1)	
Age at index procedure, median (IQR), years	64.1 (58.1–69.7)	62.3 (47.8–67.4)	0.22
BMI, median (IQR), kg/m^2	27.0 (24.3–30.6)	25.7 (22.0–29.9)	0.45
No. of polyps, median (IQR)	1 (1–1)	1 (1–2)	0.32
Largest lesion size, median (IQR), mm	20 (15–30)	27.5 (20–35)	0.18

BMI, body mass index; IBD, inflammatory bowel disease; IQR, interquartile range.
[1]Data missing for one patient in the control group.
[2]Data missing for two patients in the control group.

47.5%). Upon histologic examination, 91.0% of lesions exhibited low grade features (i. e. tubular adenomas with low grade dysplasia or sessile serrated lesions: IBD 91.3%, non-IBD 90.9%), and 9.0% exhibited high grade features (i. e. high grade dysplasia or invasive carcinoma: IBD 8.7%, non-IBD 9.1%). The distributions of lesion sizes, locations, morphology, and dysplasia grades were similar among both groups (▶ **Table 1, Table 2**). Additional lesion characteristics and procedural details are presented in **Table 1s** and **Table 2s** in the online-only Supplementary material.

Primary outcome

Overall, recurrence was detected and confirmed by histology in 21.9% of lesions. Recurrence occurred in 30.4% of IBD-associated lesions (7/23) compared with 20.9% of controls (39/187; OR 2.51, 95%CI 0.59–10.71).

In univariate analysis, lesion size (OR 1.29 per 5-mm increase, 95%CI 1.10–1.52) and presence of high grade dysplasia or invasive carcinoma (OR 5.20, 95%CI 1.22–22.19) were associated with recurrence.

Multivariate mixed effects logistic regression analysis accounting for the presence or absence of IBD, lesion size, degree of dysplasia, and procedure year (▶ **Fig. 2**) indicated that IBD was independently associated with recurrence (OR 3.08, 95%CI 1.04–9.13). Size was also associated with recurrence; each incremental 5-mm increase in lesion diameter increased the likelihood of recurrence by 32% (OR 1.32, 95%CI 1.12–1.56).

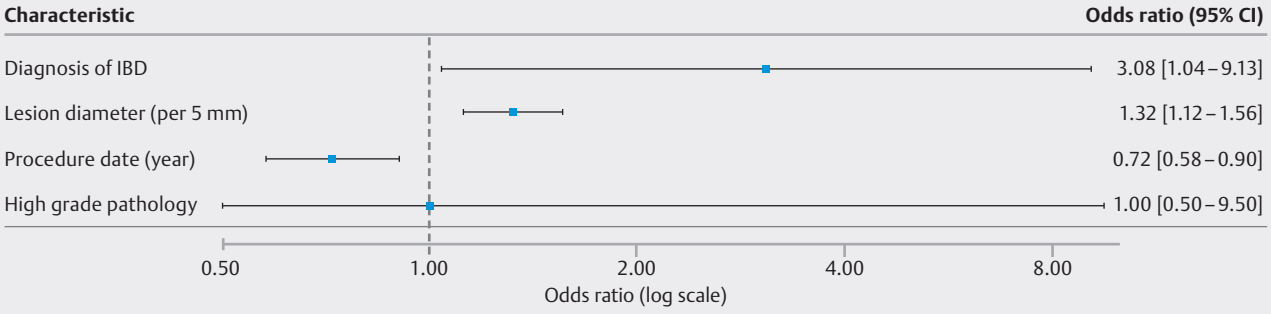
In an exploratory analysis adjusting the multivariate analysis for procedural factors, the odds of recurrence remained significantly elevated for those with IBD after adjusting for use of viscous or blue dye lifting agents (OR 3.32, 95%CI 1.08–10.25) and snare tip coagulation of margins (OR 3.00, 95%CI 1.01–8.90). However, the likelihood of recurrence for the IBD group was attenuated (OR 2.42, 95%CI 0.79–7.46) after adjusting for en bloc resection.

On a per-patient basis, recurrence occurred in 6/14 patients (42.9%) with IBD and 35/141 (24.8%) without IBD.

▶ **Table 2** Lesion-level characteristics of premalignant colorectal laterally spreading lesions resected with endoscopic mucosal resection in patients with inflammatory bowel disease compared with controls.

	Total N = 210 (100%)	Control N = 187 (89.0%)	IBD N = 23 (11.0%)	*P* value
Location within colon,[1] n (%)[1]				0.31
▪ Ascending colon	69 (35.8)	61 (35.3)	8 (40.0)	
▪ Transverse colon	44 (22.8)	40 (23.1)	4 (20.0)	
▪ Cecum	29 (15.0)	28 (16.2)	1 (5.0)	
▪ Sigmoid colon	19 (9.8)	18 (10.4)	1 (5.0)	
▪ Descending colon	14 (7.3)	12 (6.9)	2 (10.0)	
▪ Rectum	11 (5.7)	9 (5.2)	2 (10.0)	
▪ Ileocecal valve	7 (3.6)	5 (2.9)	2 (10.0)	
Lesion dysplasia, n (%)				0.73
▪ LGD	191 (91.0)	170 (90.9)	21 (91.3)	
▪ HGD	14 (6.7)	12 (6.4)	2 (8.7)	
▪ Invasive cancer	5 (2.4)	5 (2.7)	0 (0.0)	
Index lesion size ≥20 mm, n (%)	111 (55.8)	96 (54.5)	15 (65.2)	0.40
Lesion size,[2] median (IQR), mm	20 (12–30)	20 (12–30)	25 (12–30)	0.64

HGD, high grade dysplasia; IBD, inflammatory bowel disease; IQR, interquartile range; LGD, low grade dysplasia.
[1]Data based on N = 193 (Total group), N = 173 (Control group), N = 20 (IBD group).
[2]Data based on N = 199 (Total group), N = 176 (Control group), N = 23 (IBD group).



▶ **Fig. 2** Mixed effects logistic regression estimating odds of recurrence after endoscopic mucosal resection of colorectal laterally spreading lesions with premalignant potential. Presence or absence of inflammatory bowel disease, lesion size, year of procedure, and degree of dysplasia were included in the analysis.

Secondary outcomes

En bloc resection was less frequent in the IBD group (2/23 [8.7%], 95%CI 1.1%–28.0%) vs. controls (106/187 [56.7%], 95% CI 50.4%–65.2%). Surgical resection was required for 2 IBD-associated lesions (8.7%, 95%CI 1.1%–28.0%) and 7 controls (3.7%, 95%CI 1.6%–7.9%). Adverse events occurred in 5.2% and did not differ by presence of IBD (IBD 8.7%, non-IBD 4.8%) (▶ **Table 3**). The most common complications were bleeding (2.4%) and post-polypectomy syndrome (1.0%). One patient without IBD and no patients with IBD required admission for longer than 24 hours.

Discussion

EMR is a well-established method for resection of colorectal premalignant LSLs. Compared with surgical resection, EMR achieves a similarly low rate of colorectal cancer progression despite an increased risk of endoscopic recurrence [7]. This necessitates close surveillance to detect and treat recurrent lesions and prevent progression. Chronic intestinal inflammation in IBD presents several challenges to endoscopic resection. Distortion of mucosal appearance and architecture impairs the separation of lesion borders from the surrounding tissue, and epithelial fibrosis and scarring impair the endoscopist's ability

▶ **Table 3** Secondary outcomes of colorectal endoscopic mucosal resection procedures for premalignant laterally spreading lesions in patients with inflammatory bowel disease compared with controls.

	Total N = 210 (100%)	Control N = 187 (89.0%)	IBD N = 23 (11.0%)	*P* value
En bloc resection, n (%)	108 (51.4)	106 (56.7)	2 (8.7)	<0.001
Any adverse events, n (%)	11 (5.2)	9 (4.8)	2 (8.7)	0.48
▪ Bleeding	5 (2.4)	5 (2.7)	0 (0.0)	0.89
▪ Post-polypectomy syndrome	2 (1.0)	1 (0.5)	1 (4.3)	0.15
▪ Other,[1] n (%)	4 (1.9)	3 (1.6)	1 (4.3)	0.40
Surgery required for definitive treatment, n (%)	9 (4.3)	7 (3.7)	2 (8.7)	0.34
Procedure time, median (IQR), minutes[2]	68 (52–89)	68 (51–86)	72.5 (60–108)	0.20

IBD, inflammatory bowel disease; IQR, interquartile range.
[1]Other adverse events include hypoxia and abdominal pain. No perforations occurred in the study.
[2]Procedure time is summarized per procedure (not per lesion).

to lift the lesion from the submucosal layer and firmly grasp the tissue with a snare device. With improvements in endoscopic imaging (i. e. high definition white-light endoscopy, chromoendoscopy), endoscopic resection has begun to establish itself as the first-line therapy for LSLs in IBD [5, 9].

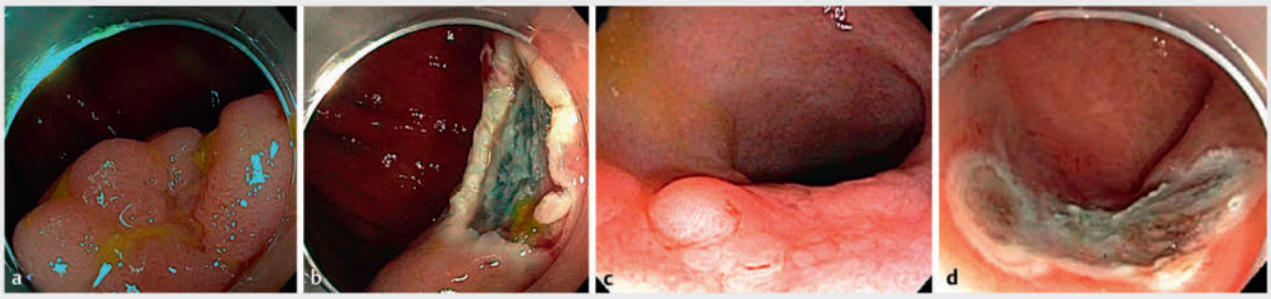
In the current study, we aimed to compare performance of EMR for LSLs among those with and without IBD. After accounting for variability in lesion size and degree of dysplasia in a mixed effects logistic regression model, the odds of recurrence appeared elevated for those with IBD vs. without IBD.

The recurrence rate among LSLs in the cohort without IBD was 20.9%, which is similar to the literature-reported rate of 15% in the general population [10]. In contrast, the recurrence rate among IBD-associated LSLs in our study was 30.4%.

There are many factors that may impact lesion recurrence after EMR. It is possible that the higher rate of en bloc resection in our control group was in part responsible for the lower recurrence rate compared with the IBD group. However, it is also probable that other factors may have contributed to recurrence. Our data collection took place over a period of 6 years, during which EMR techniques have evolved. Subtle changes in techniques may be difficult to capture in retrospective studies. Additionally, the pathophysiologic nature of the underlying disease process might stimulate recurrent neoplasia to a greater extent than in those without IBD. One emerging technique has been the use of thermal ablation of the defect margin. A prospective controlled study has indeed shown that this can reduce recurrence rate from 21% to 5.2% [11]. Cold snare EMR is another technique that has recently gained popularity for resection of flatter lesions such as sessile serrated lesions or other flat polyps. Data for this technique are limited for larger LSLs, though some prospective data have shown much lower rates of recurrence with cold snare EMR, as low as 1.7% [12]. Several studies have shown a lower rate of recurrence with underwater EMR compared with conventional EMR, as demonstrated in a meta-analysis [13].

In order to account for the potential impact of these various techniques on recurrence after EMR, we conducted an exploratory analysis adjusting the multivariate model for factors such as ablation of margins and use of specific lifting agents. After individually introducing these factors into the multivariate model, we found that the odds of recurrence remained significantly elevated for those with IBD after adjusting for use of viscous or blue dye lifting agents (OR 3.32, 95%CI 1.08–10.25) and snare tip coagulation of margins (OR 3.00, 95%CI 1.01–8.90). However, the difference between the IBD-associated and non-IBD-associated lesions was attenuated when adjusting for en bloc resection. These exploratory analyses should be interpreted with caution given the limited sample size of the study. Dysplastic lesions in IBD present several challenges to complete endoscopic resection. Mucosal inflammation in IBD leads to clustered development of dysplasia in regions of active or prior colitis [4]. This can result in lesions with coalescing borders, indistinct margins, and nonpolypoid morphology upon endoscopic visualization [8]. Furthermore, adequate submucosal tissue lift to elevate and separate the lesion from the surrounding mucosa is a prerequisite for en bloc resection with EMR. In the setting of colitis, longstanding epithelial inflammation leads to progressive submucosal fibrosis [8], which impedes the duration and quality of lift that is possible to achieve during EMR (▶ **Fig. 3**).

Although ESD has been shown to achieve higher en bloc resection rates and lower recurrence rates compared with EMR [14, 15], it continues to face barriers to widespread implementation due to lack of training opportunities, added risk, and procedural duration, thereby limiting availability of the procedure. Concurrent inflammation and fibrosis in IBD-associated lesions also adds to the difficulty of performing ESD. Further improvements in EMR should be directed toward border incision techniques prior to snaring ("hybrid-ESD") and submucosal lifting solutions that perform well with surrounding inflammation and fibrosis.



▶ **Fig. 3** Colorectal laterally spreading lesions before and after endoscopic mucosal resection, with and without inflammatory bowel disease (IBD). Control LSL: a well-defined borders and slightly raised, with good submucosal uptake of lifting solution; b clean resection bed. IBD-associated LSL: c flat and irregular with ill-defined borders, with poor uptake of lifting solution; d after resection.

Our primary limitation was the small sample size, which reduced our power to detect potential differences in recurrence between patients with and without IBD. The association between recurrence and IBD only reached statistical significance when adjusted for lesion size and histologic severity. Interestingly, this association (IBD and recurrence) was no longer significant in the exploratory analysis adjusting for en bloc vs. piecemeal resection. Nevertheless, while prior work has explored the risk of recurrence following endoscopic resection of polyps in the setting of IBD [16, 17, 18], our study has the advantage of a well-characterized control group, which allowed us to control for size and grade of dysplasia. It is also among the first studies since the SCENIC guidelines to report on the impact of newer strategies for attempting endoscopic removal of LSLs in patients with IBD. While endoscopic approaches are much less invasive than surgery, our findings suggest that more vigilant monitoring for recurrence should be considered in patients with IBD following endoscopic removal of neoplastic lesions in regions of disease. This is particularly important if en bloc resection is not possible. Other limitations include the retrospective study design and variability in the follow-up duration. Another consideration is that patients with IBD may develop polyps in uninvolved regions (i. e. right-sided polyps in those with distal colitis). These lesions are not likely to be subject to the chronic inflammatory changes that make resection challenging and would be more accurately classified as non-IBD polyps. In our series, the majority of lesions (83%) were confirmed to be in regions of prior inflammation, with the remaining patients having a history of pancolitis. Given these limitations, our findings need to be interpreted as preliminary and require further confirmation.

In summary, we found a trend toward greater histologic recurrence after EMR of premalignant LSLs for those with IBD compared with those without IBD. The association was significant after adjusting for lesion size and degree of dysplasia. Piecemeal resection during EMR of LSLs is more frequently employed in IBD, which is a substantive factor. Further refinement of EMR-based techniques (e. g. underwater EMR, hybrid-ESD) may improve en bloc resection rates and reduce recurrence of premalignant LSLs in IBD. EMR in patients with IBD should continue to be performed in expert centers for patients willing to participate in a rigorous surveillance program. Future large prospective studies are necessary to corroborate the study findings and explore important technical factors, including en bloc resection.

Conflict of Interest

The authors declare that they have no conflict of interest.

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