Endoscopic Management of Complex Lesions in Patients With Inflammatory Bowel Disease

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Abstract: Patients with inflammatory bowel disease (IBD) have a higher risk of developing colitis-associated dysplastic lesions. Surveillance colonoscopy with endoscopic imaging techniques such as chromoendoscopy has been suggested. However, complex dysplastic lesions of larger size, challenging location behind folds, and nonpolypoid morphology defy standard polypectomy techniques and require advanced management with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). When technically feasible for visible dysplasia with distinct margins, these endoscopic procedures have replaced the traditional approach of surgical management. Recent guidelines support careful endoscopic inspection of the colonic mucosa with high-definition colonoscopes and the application of imaging techniques such as chromoendoscopy to enhance lesion detection and characterization as well as to help determine whether endoscopic management is an effective alternative to colectomy. Endoscopic resection techniques such as EMR and ESD have become key modalities in the management of endoscopically resectable dysplasia in patients with IBD.

Keywords
Inflammatory bowel disease, dysplasia, surveillance, endoscopic mucosal resection, endoscopic submucosal dissection

Patients with inflammatory bowel disease (IBD), either ulcerative colitis (UC) or Crohn's colitis, are at significantly higher risk for the development of colitis-associated dysplastic lesions and colorectal cancer. This risk increases with duration and extent of disease, persistent inflammatory activity, prior dysplasia, and coexistent primary sclerosing cholangitis.[1-6] Colorectal cancer in patients with IBD arises from dysplastic tissue. However, unlike sporadic colorectal cancers that develop from the adenoma-carcinoma sequence, IBD-related cancers can develop in the background of chronic inflammation and regeneration.[7,8]

Nonpolypoid lesions, including flat and depressed colorectal lesions, are relatively common in average-risk patients, with an overall prevalence of 9.35% and a greater association with carcinoma than polypoid lesions.[9] Polypoid and nonpolypoid dysplastic lesions have been identified with increasing frequency in average-risk patients as well as in patients with IBD.[7,9]

Some of these lesions can defy colonoscopy resection by standard snare polypectomy technique due to various factors, including

challenging location behind the folds, size above 2 cm, and unfavorable sessile or flat morphology. The endoscopist also may view removal as unsafe. These lesions, known as complex polyps and also referred to as defiant polyps by some endoscopists,[10-12] will undergo photo documentation and tissue sampling. They are referred to expert advanced endoscopists for curative colonoscopic resection using endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). Based on numerous studies, most dysplastic lesions in average-risk patients can be successfully eradicated with dedicated therapeutic colonoscopy using adjunctive resection and ablation techniques, including EMR and ESD.[10,13-19]

The use of EMR and ESD has been rising in the United States.[19,20] EMR has been considered the first-line treatment for all large, flat, and sessile lesions otherwise referred for standard snare polypectomies. ESD can be used for lesions that are either partially lifting or completely nonlifting due to the submucosal fibrosis from chronic inflammation, as well as for lesions that are larger than 2 cm.[20]

Many dysplastic lesions seen in the setting of long-term IBD are considered complex because of their morphology, location, and the underlying chronic inflammatory process that results in submucosal fibrosis. The identification of subtle morphologic features of the lesions also can be difficult when active disease is present. In the past, most patients with IBD who had dysplastic lesions were referred for colectomy.[21] This approach has evolved over the past decade to EMR and ESD prior to colectomy referral.[7,22-24]

Recent epidemiologic studies in patients with long-term IBD have estimated the pooled incidence of colorectal cancer after endoscopic resection of dysplastic lesions to be 5.3 cases per 1000 patient-years, whereas the incidence of interval colorectal cancer is estimated to be 2.5 cases per 1000 patient-years.[25,26] The current guidelines on the management of dysplasia in patients with IBD advocate a similar approach to that recommended for average-risk patients if the colonic lesion is deemed to be endoscopically resectable, with clear borders and no submucosal invasion.[7,22,23,27] This article reviews the currently available evidence and shortcomings of the endoscopic management of complex lesions in patients with IBD.

Identification of Dysplastic Lesions in Inflammatory Bowel Disease Amenable to Endoscopic Treatment

The international consensus statement (endorsed by the American Gastroenterological Association and American Society for Gastrointestinal Endoscopy [ASGE]) on surveillance and management of dysplasia in IBD, known as the SCENIC consensus, has simplified endoscopic classification of dysplastic lesions and their management.[22,23] The revised Paris classification should be applied to IBD patients to classify lesions as polypoid (pedunculated, sessile) and nonpolypoid (slightly elevated, flat, depressed). Additional endoscopic features, such as location of the lesion within or outside an area of known colitis, borders (distinct or indistinct), and the presence of ulceration, and other features of submucosal invasion, need to be included as well. The term dysplasia-associated lesion or mass has been retired by gastrointestinal pathologists and replaced by the modified Paris classification.[8] Optimal characterization of a lesion's borders is of key importance to determine whether endoscopic removal of the lesion can be attempted.

Imaging techniques, such as dye-based chromoendoscopy and virtual chromoendoscopy with narrow-band imaging, have become available to improve the characterization of complex lesions in patients with IBD. High-definition colonoscopes offering virtual chromoendoscopy have become the standard of care in most endoscopic centers.

The SCENIC consensus statements recommend the use of chromoendoscopy techniques with older-generation, standard-definition colonoscopes but also with newer, high-definition colonoscopes.[22,23] Since the publication of these recommendations in 2015, newer data supporting either dye-based chromoendoscopy for dysplasia detection or high-definition colonoscopy with virtual chromoendoscopy have emerged.[28-30] The use of virtual chromoendoscopy with narrow-band imaging was found to be beneficial, whereas no benefit was found in earlier studies of virtual chromoendoscopy with narrow-band imaging in comparison to conventional colonoscopies for dysplasia detection.[31-34] All of these changes were reflected in the latest American College of Gastroenterology (ACG) guidelines on UC, which recommend the use of chromoendoscopy in patients undergoing surveillance colonoscopy when using standard-definition colonoscopy.[7] On the other hand, when using high-definition colonoscopy in patients with UC, white-light endoscopy with narrow-band imaging or dye-based spray chromoendoscopy has been suggested.[7]

Several imaging classifications of pit patterns and capillary patterns have been used, including the Kudo pit pattern, Narrow-Band Imaging International Colorectal Endoscopic Classification, and Sano microvascular classification; however, they have not been fully validated in patients with IBD.[35-37]

A multicenter study by Bisschops and colleagues[38] assessed the diagnostic accuracy and interobserver agreement of Kudo pit pattern classifications in patients with long-term UC undergoing surveillance using either

traditional methylene blue chromoendoscopy or virtual chromoendoscopy with narrow-band imaging. The overall interobserver agreement among experienced endoscopists for any pit pattern was only fair; however, differentiation between nonneoplastic and neoplastic pit patterns in UC lesions showed a moderate to substantial agreement among expert endoscopists. The agreement for differentiating neoplastic from nonneoplastic lesions is significantly better for narrow-band imaging compared with chromoendoscopy. The assessment of a pit pattern I or II with nonmagnified chromoendoscopy or narrow-band imaging has a high negative predictive value to rule out neoplasia.

A recent systematic review and meta-analysis for the diagnostic accuracy of in vivo lesion characterization in colonic IBD using optical imaging techniques analyzed all available imaging techniques, including virtual chromoendoscopy, dye-based chromoendoscopy, magnification endoscopy, and confocal laser endomicroscopy.[39] Most studies reviewed in the analysis used the Kudo pit pattern when characterizing dysplastic lesions. Real-time Kudo pit patterns appeared to have a reasonable specificity of 89% (95% CI, 80%-94%) but a sensitivity of 78% (95% CI, 57%-91%). The varying degree of mucosal inflammation contributes to challenging pit-pattern and vasculature interpretation in patients with IBD. Real-time confocal laser endomicroscopy was determined to be a highly accurate technology for differentiating neoplastic from nonneoplastic lesions in patients with colonic IBD.[39] However, most confocal laser endomicroscopy studies were performed by single expert users within tertiary centers, potentially confounding these results.[39]

The most recent attempt to improve recognition and classification of dysplastic lesions for the diagnosis of dysplasia in IBD using imaging modalities involves the introduction of a new endoscopic classification: Frankfurt Advanced Chromoendoscopic IBD Lesions (FACILE) classification.[40] The sensitivity, specificity, and accuracy with high confidence for FACILE classifications were 72%, 90%, and 76%, respectively. Flat shape, irregular surface, vascular patterns, and signs of inflammation predicted dysplasia.[40] The diagnostic performance of all nonexpert participants improved after a training module.

Although all of these endoscopic techniques improve lesion characterization in patients with IBD, their accuracy remains lower than in average-risk patients. Persistent inflammation may interfere with adequate assessment. In any event, all of these recent developments, culminating in the current SCENIC and ACG guidelines, have led to increased awareness regarding recognition of complex lesions in patients with long-term IBD and implementation of adequate classification followed by referral to tertiary centers for further endoscopic management when indicated.

Endoscopic Resection of Identified Lesions in Patients With Inflammatory Bowel Disease

The SCENIC international consensus recommendations suggest that all visible lesions with clearly defined borders and without endoscopic features of submucosal invasions or ulcerations should be considered for endoscopic resection by an experienced endoscopist.[22,23] The SCENIC criteria for endoscopic resection include the following steps: identification of distinct margins of the lesions, complete removal confirmed on visual inspection after endoscopic resection, histologic examination of the resected specimen to confirm that it is consistent with complete removal, and biopsy of specimens from mucosa immediately adjacent to the resection site to confirm that the site is free of dysplasia per histologic examination. Careful endoscopic surveillance has been recommended as well. After the endoscopic removal of the lesions, the site should be marked with a tattoo to facilitate future follow-up surveillance.[22] The recent ACG guidelines also advocate for thorough endoscopic evaluation of the lesions followed by removal of all endoscopically discrete lesions and ongoing surveillance rather than surgery.[7] However, the current ACG guidelines, supported by recent studies,[41,42] state that obtaining biopsy specimens from mucosa surrounding the resection site may no longer be necessary, given a very low yield of detecting dysplasia.[7]

Colitis-associated dysplastic lesions are especially challenging. They all have a certain degree of submucosal fibrosis due to chronic inflammation, which does not allow a typical approach with standard snare polypectomy techniques and requires more advanced techniques with EMR or ESD. The nature of the lesions carries a greater risk of incomplete resection and procedure-related complications. Thus, these lesions should be truly identified as complex lesions.

The endoscopic resection techniques of EMR and ESD have been used for many years to manage large colorectal lesions. The efficacy and safety of their use in average-risk patients have been confirmed by numerous studies.[10,13-18] On the other hand, the data for overall evidence of efficacy and safety of these techniques in patients with IBD have been sparse, although more are emerging. The optimal choice of technique varies depending on the endoscopist's skills and the lesion's features. Endoscopic techniques applied to colitis-associated dysplastic lesions in IBD recently have been discussed in the Interventional IBD position statement from the Global Interventional IBD Group.[24]

In EMR, a previously identified lesion with distinct borders is lifted with a submucosal injection and then resected with a hot snare in piecemeal or en-bloc fashion. In ESD, the borders of the lesion are analyzed, and the

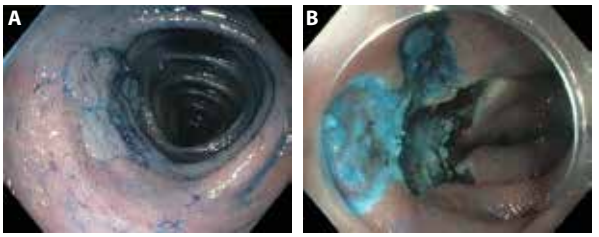

Figure 1. High-grade dysplastic lesion in a patient with IBD pre-EMR (**A**) and post-EMR (**B**).

EMR, endoscopic mucosal resection; IBD, inflammatory bowel disease.

edges are marked with a snare tip in a soft coagulation mode. Subsequently, the lesion is injected. In contrast to EMR, ESD involves careful submucosal dissection beneath the lesion with an electrosurgical knife, and the underlying submucosa is incised.

Various dissection techniques have been summarized in the position statement from the Global Interventional IBD Group.[24] These include the traditional approach of dissecting the submucosal plane from one side to the other side. When submucosal fibrosis is encountered, the submucosal tunnel technique is recommended. Additionally, the so-called hybrid ESD or simplified ESD technique has been emphasized when there is inadequate submucosal dissection. This technique can be a bridge between EMR and full ESD for lesions up to 4 cm and includes steps such as an incision in the submucosal plane and resecting the remaining dysplastic tissue with a snare technique.

The hybrid ESD technique has been time-consuming and was thought to be associated with a higher risk of complications compared with traditional EMR and ESD; however, the estimated complication rate of hybrid ESD recently has been reported to be comparable to that of full-ESD clips closure,[43] and endoscopic suturing has been demonstrated to effectively manage perforation during the procedure. Complete closure of submucosal dissection sites can be achieved in certain circumstances.[19] In addition, careful coagulation of vessels at the dissection site may minimize any potential bleeding.[19]

When choosing between EMR and ESD in patients with IBD, lesion size exceeding 2 cm and presence of scarring of the colon from chronic colitis leading to a nonlifting effect are important factors favoring use of ESD for sessile and flat lesions. EMR also can be limited regarding reliable, complete resection of polyps larger than 2 cm. It is estimated that only 47% to 63% of polyps larger than 2 cm will be removed completely by EMR en bloc.[44] Piecemeal resection has become the common EMR approach despite a higher risk of recurrence.[44]

Kinoshita and colleagues[45] demonstrated that almost all resected lesions in patients with IBD had submucosal fibrosis contributing to nonlifting or partial lifting. When performing EMR for lesions larger than 2 cm, piecemeal resection may be unavoidable. According to Bang and Bourke,[46] EMR can have a 10% to 15% recurrence rate. In contrast, ESD techniques have a recurrence rate of only 2%. Suzuki and colleagues[47] described multicenter experiences of ESD of 32 ulcerative colitis–associated lesions. Submucosal fibrosis and adipose deposition were observed in 31 (97%) and 13 lesions (41%), respectively, and en-bloc resection was possible in 29 of 32 lesions (91%), with minimal complications (bleeding) reported in 1 patient.

In a meta-analysis by Wang and colleagues,[6] ESD offered a significantly higher rate of en-bloc resection and a lower recurrence rate compared with EMR in average-risk patients. However, ESD had a higher rate of procedure-related complications and was more time-consuming to perform than EMR.

Shen and colleagues[24] reported that endoscopic resection can be described as an immediate success with a complete resection and clearance of margins, a mid-term success with the absence of recurrent dysplasia on a follow-up colonoscopy, and a long-term success with avoidance of surgical management with colectomy.

Thus far, there have been small studies on the efficacy and safety of endoscopic resection reported in the recent IBD literature. In a study by Hurlstone and colleagues[48] in which EMR and ESD were compared in the examination of 135 lesions in the setting of long-term UC, no difference in adverse events was seen between the study and control groups. A recent cohort series from the United Kingdom[49] reported that endoscopic resection of 15 large lesions associated with colitis is feasible and safe

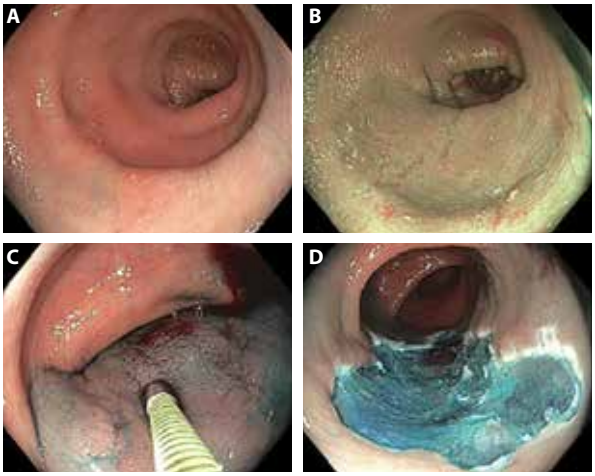

Figure 2. A: White-light high-definition view of a low-grade dysplastic lesion in a patient with IBD. **B:** Narrow-band imaging of the lesion. **C:** The lesion undergoing EMR. **D:** The post-EMR site.

EMR, endoscopic mucosal resection; IBD, inflammatory bowel disease.

Table. Studies Investigating the Safety and Feasibility of Endoscopic Resection (EMR and ESD) in Patients With IBD

Study	Endoscopic Technique	Study Design	Number of Patients/ Number of Lesions	Lesion Size in mm (range)	Number of Resected Lesions	Adverse Events, n and/or %	Recurrence
Hurlstone et al[48]	EMR/ESD	Prospective case-control	712 UC/ 135	Median: 8 (2-24)	132	No differences between groups	Not included
Smith et al[56]	Hybrid ESD	Prospective cohort	67 UC/ 67	Median: 15 (4-38)	67	Bleeding: 7 Perforation: 2	Not included
Iacopini et al[57]	ESD	Prospective cohort	9 UC/ 10	Median: 32.5 (20-50)	7	Bleeding: 2 (10%)	2/10
Suzuki et al[47]	ESD	Retrospective cohort	32 UC/ 32	Median: 33.5 (14-73)	29	Bleeding: 1 (3%)	1/26
Kinoshita et al[45]	ESD	Retrospective cohort	25 UC/ 25	Mean: 21.6 ±12.8[a]	25	Perforation: 1 (4%)	0
Gulati et al[49]	ESD	Prospective cohort	15 UC/ 15	Mean: 48.3 ±21.7[a] (20-90)	14	Perforation: 1	Not included
Alkandari et al[51]	ESD/EMR	Retrospective cohort	93 UC/ 119	≤20 (n=67) >20 (n=52)	119	Perforation: 4 Bleeding: 3	7/119
Yadav et al[50]	EMR/ESD	Retrospective cohort	63 UC, 27 CD, 7 IC/ 97	<20 (n=68) ≥20 (n=56)	124	Bleeding: 3	20/124
Yang et al[55]	ESD	Retrospective cohort	25 IBD/ 25	Median: 23 (12-48)	15	0	2/15
Buchner et al[53]	EMR	Retrospective cohort	44 UC, 26 CD/ 70	Median: 18.3 (10-80)	53	Bleeding: 3	5/39

CD, Crohn's disease; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; IBD, inflammatory bowel disease; IC, ischemic colitis; UC, ulcerative colitis.

[a]Standard deviation.

with an array of resection methods when performed by advanced endoscopists. In a retrospective review of 124 lesions in 97 patients with IBD undergoing surveillance colonoscopy with ESD and EMR, Yadav and colleagues[50] demonstrated efficacy and safety in the settings of long-term IBD, but EMR was associated with a higher recurrence rate compared with ESD.

A recent multicenter retrospective cohort study from Europe that reported outcomes of endoscopic resection of 119 lesions in 93 patients concluded that ESD best treats larger lesions with submucosal fibrosis. In comparison, smaller lesions without significant submucosal fibrosis are best managed by EMR.[51] In this study, the recurrence rates of EMR and ESD were reported to be 7% and 9%, respectively, although a prior meta-analysis reported a higher rate of recurrence, 13.8%, following EMR in non-colitis-associated lesions.[51,52]

My colleagues and I conducted a cohort study of 70 patients with IBD who had 53 complex or defiant lesions.[53] We found that most of these lesions were eradicated during therapeutic colonoscopy with chromoendoscopy and dedicated EMR. The rate of local residual dysplasia at the resection site was 12.8%, which underscores the importance of close follow-up after colonoscopy resection of complex or defiant lesions. Figures 1 and 2 demonstrate representative colonic lesions in patients with IBD.

Kinoshita and colleagues[45] analyzed short- and long-term outcomes of colorectal ESD in 25 patients with UC and concluded that ESD was feasible when performed by expert endoscopists. The procedure time was relatively long (mean of 71 minutes), but no recurrence occurred during 21 months of follow-up. Interestingly, the study showed that prediagnosis by biopsy and endoscopy had overall low accuracy for final histology (78.2% and 76%, respectively), suggesting that diagnostic and therapeutic ESD is a desirable approach to complex lesions in IBD settings, as it may allow complete resection with much lower recurrence rates compared with piecemeal EMR. The Table lists studies evaluating the feasibility and safety of EMR and ESD in patients with IBD.

Given the relatively higher recurrence rates reported in some studies, patients should be monitored closely following endoscopic resection with repeated follow-up examinations that occur between 3 and 6 months, as recommended by SCENIC and ASGE guidelines.[22,23,27] Despite the potential advantages of endoscopic resection of dysplastic lesions in patients with IBD, the overall quality of available data is still lacking due to small sample sizes, a retrospective approach, and insufficient follow-up. Newer studies are needed to fill this gap.

In the near future, ESD could be considered an effective method of choice in the management of complex lesions in the setting of IBD; however, adequate training of ESD among endoscopists in Western countries is required. Recent reports on ESD use in Barrett esophagus confirmed that ESD techniques could be learned and applied successfully by expert endoscopists in the United States and other Western countries.[54,55]

Although EMR use has been increasing among gastroenterologists in the United States, according to recent research,[20] ESD remains a highly selective technique, not available in many centers. One of the main unresolved issues is the lack of Current Procedural Terminology codes and reimbursement for ESD, which ultimately limits its availability in many IBD centers in the United States. Because ESD may become a technique of choice for truly complex lesions associated with IBD, further training needs to be implemented and reimbursement issues resolved. Further evidence from prospective studies on ESD outcomes in the IBD setting also will support its broader application and help optimize endoscopic management of complex lesions in patients with IBD.

Conclusion

The goals for managing complex lesions in patients with IBD are to improve the detection and characterization of such dysplastic lesions and ultimately proceed to adequate endoscopic management vs referral for surgical management, followed by careful surveillance. By improving imaging techniques, training endoscopists' eyes to better detect and characterize such lesions, and learning adequate resection techniques while seeking further medical therapies for IBD patients, we are moving toward the ultimate aim of preventing cancer in patients with IBD.

Disclosures

Dr Buchner has served as a one-time consultant for Olympus on a topic unrelated to this article.

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