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Selection of EMR and ESD for Laterally Spreading Lesions of the Colon

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Abbreviations *EMR* Endoscopic mucosal resection · *ESD* Endoscopic submucosal dissection · *G-LSL* Granular laterally spreading lesion · *LSL* Laterally spreading lesion · *NG-LSL* Non-granular laterally spreading lesion · *SMIC* Submucosa-invasive cancer

Abstract

Introduction Colonic laterally spreading lesions (LSL) are increasingly managed using endoscopic methods that comprise two main techniques: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD).
Purpose of Review In this review, we aimed to review the most recent literature on selection of the best endoscopic technique in the management of colonic LSL.
Recent Findings EMR and ESD are complimentary techniques in the management of patients with colonic LSL.
Summary EMR is safe and effective in most patients with LSL, except for cancers with submucosal invasion in whom R0 resection is favored.

Introduction

Colonic laterally spreading lesions (LSL) are sessile or flat colonic lesions at least 10 mm in size and comprise approximately 1–3% of all colon polyps [1]. The European Society of Gastrointestinal Endoscopy (ESGE) and Japanese Gastrointestinal Endoscopy Society (JGES) guidelines recommend the adoption of advanced endoscopic techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for resection of LSL [2, 3]. Although there remains an ongoing debate regarding the best treatment strategy for the management of LSL, the decision should ultimately be based on the lesion pathology [1]. Herein, we will review the recent literature on the selection of the best techniques in the management of colonic LSL.

Endoscopic mucosal resection

Indications

EMR is the most suitable method for endoscopic therapy of LSL, except in patients with colorectal cancer with submucosal invasion (SMIC) as these patients generally require en bloc resection [1]. R0 resection of well-differentiated colorectal cancer with superficial submucosal invasion (defined as depth of invasion < 1000 μm) without lymphovascular involvement and tumor budding, termed low-risk SMIC, can be considered curative [1]. EMR can be performed en bloc; however, en bloc resection is limited to lesions ≤ 20 mm in the proximal colon and ≤ 25 mm in the rectosigmoid colon as R0 resection becomes more challenging and the risk of perforation increases significantly with larger LSL [2, 4]. Consequently, the inability to perform en bloc resection of larger LSL with SMIC is the main limitation of EMR compared to ESD. Regardless, SMIC occurs in only approximately 3–10% of LSL [1] and therefore predicting the risk of submucosal invasion is an important component of LSL management. Endoscopic features associated with SMIC are as follows:

(A) Non-granular surface pattern

In Western LSL cohorts, non-granular LSL (NG-LSL) comprise < 20% and it is established that NG-LSL have an overall greater SMIC risk of 10–15%. In contrast, the risk of SMIC is < 2% for granular LSL (G-LSL) [5, 6]. In a recent large prospective, observational, multicenter study comprising 2277 large colon lesions at least 20 mm in size, the presence of NG-LSL was significantly associated with an increased risk of SMIC, with odds ratio (OR) of 2.8 when compared to a G-LSL on multivariate logistic regression analysis [7•] (Fig. 1).

(B) The Paris classifications 0–Is, 0–IIa/Is, and 0–IIc and the Kudo pit pattern V

In the same study, lesions with dominant nodules (the Paris classifications 0–Is and 0–IIa + Is) were significantly associated with submucosal invasion with ORs of 2.7 and 2.4, respectively, compared to the Paris classification 0–IIa polyps. Also, the presence of 0–IIc was associated with submucosal invasion, with OR 1.8, compared to polyps without 0–IIc features [7•]. Although the Kudo type V lesions accounted for only 5% of the entire cohort, they were significantly associated with submucosal invasion, with OR 14.2, compared to the Kudo types I–IV [7•]. The diagnostic accuracy for the presence of submucosal invasion was the highest for non-granular/Paris 0–Is lesions, with accuracy of 89% (95% confidence interval 87.5–90.3%), which had a submucosal invasion risk of 15% [7•].

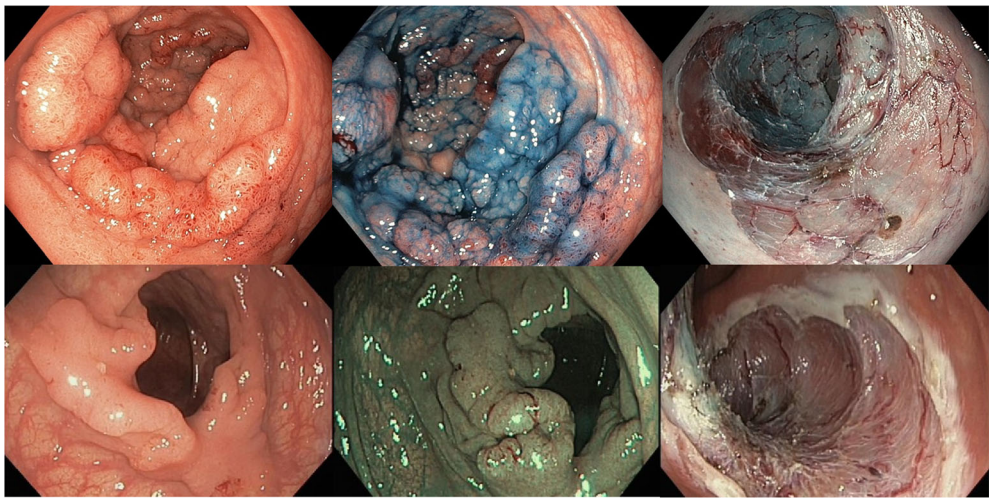

Fig. 1. Endoscopic images of granular (top panel) and non-granular LSL (bottom panel).

(C) Lesion size and site

LSL located in the rectosigmoid colon are at increased risk of SMIC, with OR 1.9. Larger lesions were also more likely to have submucosal invasion at the time of resection, with OR 1.1 for every 10-mm increase in lesion size [7•]. En bloc resection of LSL with low-risk SMIC offers potential for cure and avoidance of surgery. The potential clinical benefit of endoscopic cure is maximal in the distal colon and rectum as the perioperative risk and post-surgical morbidity are the greatest at this site [8]. As a result, ESD is most likely to confer a meaningful advantage when performed in the rectosigmoid colon.

Treatment success

EMR is highly effective in the treatment of large LSL. In a meta-analysis of 50 studies comprising 6442 patients, the pooled treatment success rate was 90.3% and only 8% of patients required surgical resection for failed endoscopic therapy [1, 9] (Fig. 2).

However, EMR can be challenging in patients with LSL which fail to lift with submucosal injection. This can occur due to the presence of fibrosis in the submucosal space, which in turn can result from prior biopsies, injection of carbon suspension for marking, lesion biology, or prior attempts at polyp resection. A technique known as "cold-forceps avulsion with snare tip soft coagulation" (CAST) has been proposed for non-lifting LSL. In a prospective, comparative study, patients with non-lifting lesions undergoing CAST had similar outcomes to those undergoing conventional EMR for lifting LSL, with no significant difference in treatment success or adverse event rates between the two cohorts [10].

Recurrence

Another major limitation of EMR compared to ESD is the significant recurrence rate of 10–15% [9]. The size, morphology, site, and access (SMSA) score, which consists of four levels (levels 1 to 4), has been proposed to predict clinical

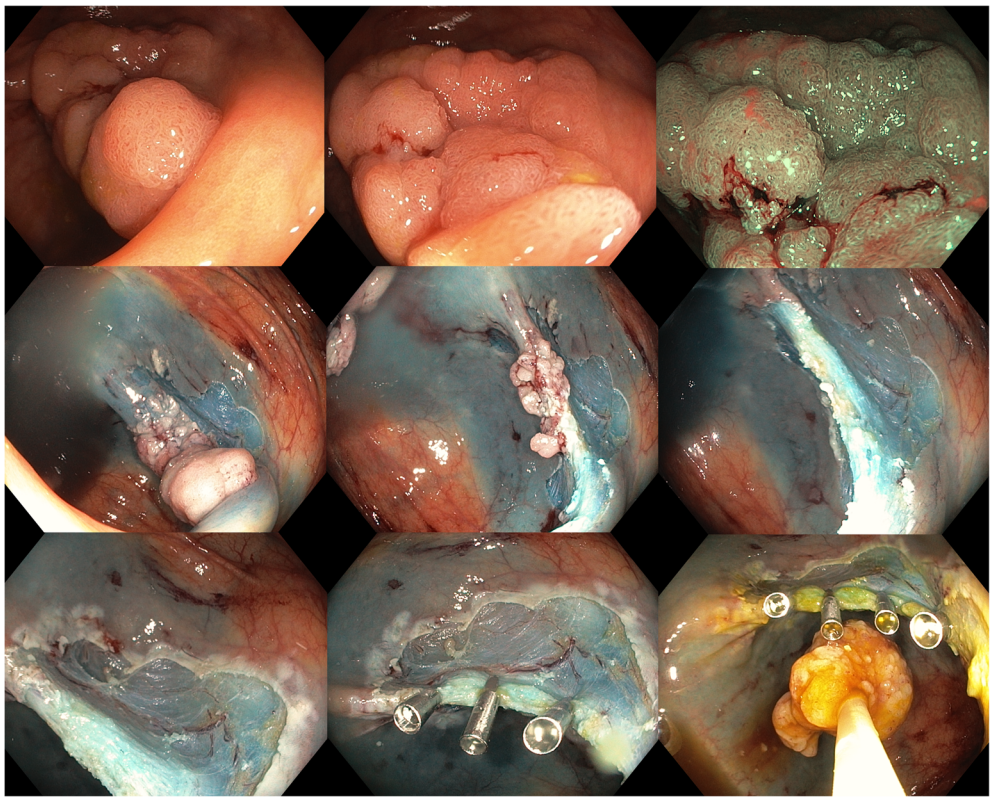

Fig. 2. EMR of a granular, 50 mm cecal polyp, with the Paris 0–IIa + Is and the Kudo IV features. Endoscopic clips were placed for type II deep mural injury during the procedure. The final histology showed mixed tubular adenoma and traditional serrated adenoma.

outcomes following EMR. In this scoring system, the highest scores are allocated for lesions > 40 mm in size, flat polyp morphology, polyps located in the right colon, and polyps in difficult locations such as around the appendiceal orifice or involving the ileocecal valve [11]. This scoring system was validated in a large retrospective study of 2675 patients, where the highest SMSA level (level 4) was associated with a significantly higher risk of lesion recurrence on follow-up at 23.5%, compared to 5.5% and 9.2% for SMSA levels 2 and 3, respectively ($p < 0.001$).

The risk and time course of recurrence can be stratified. In the two-phase Sydney EMR Recurrence Tool (SERT) study, a lesion size of ≥ 40 mm, occurrence of significant intraprocedural bleeding, and high-grade dysplasia were associated with polyp recurrence on multivariate logistic regression analysis. The absence of all of these three factors was associated with a recurrence rate of only 8.7% compared to recurrence rate of 25.9% when any one of these factors were present [12].

Soft coagulation cauterization of the post-EMR resection margin using the tip of a snare (technique known as "snare tip soft coagulation") at the time of the initial EMR has been shown to decrease the risk of recurrence and the final publication of this study is awaited [13]. Moreover, recurrence is usually diminutive and easily treated, such that in long-term follow-up > 98% of patients are adenoma-free and considered cured [14].

Biopsy of the post-EMR scar is routinely performed to detect residual or recurrent polyp. However, endoscopic examination of the scar using high-definition white light and narrow-band imaging has been shown to be very accurate at detecting residual/recurrent polyp, with accuracy of 94%, sensitivity of 93.3%, specificity of 94.1%, and negative predictive values of 98.5% [15]. Therefore, routine biopsy of the post-EMR scar is likely not required if careful endoscopic examination is performed during follow-up and no demarcated areas of neoplastic pit pattern are seen.

Adverse events

EMR of large LSL is safe, with relatively low adverse event rates. In a recent meta-analysis of 6442 patients, the pooled rates of bleeding, perforation, and procedure-associated mortality were 6.5%, 1.5%, and 0.08%, respectively [9]. If any significant bleeding is encountered during the procedure (i.e., lasting longer than 60 s), direct application of soft coagulation via the snare tip (80 W, effect 4) to the site of bleeding has been shown to be successful in inducing hemostasis in 91% of cases [16]. Also, patient and lesion characteristics with increased likelihood of procedure-related bleeding can be predicted. In a large retrospective study of 2012 patients undergoing EMR of large LSL, the following four factors were associated with increased risk of bleeding post-EMR: (1) LSL size > 30 mm, (2) LSL located in the cecum, ascending colon, or hepatic flexure, (3) presence of any significant medical conditions, and (4) lack of epinephrine in the submucosal injectant solution. The presence of at least three of these four factors was associated with a bleeding rate of 17.5% [17]. In another large retrospective study from Europe comprising 1214 patients undergoing EMR for large LSL, in addition to the large lesion size (≥ 40 mm) and right-sided LSL, other factors associated with procedure-related bleeding were concurrent aspirin administration, lack of clip placement post-EMR, and American Society of Anesthesiologists (ASA) class III or IV [18]. However, the application of prophylactic clips to the resection bed has not been shown to be cost-effective in the prevention of post-EMR bleeding [19]. Moreover, the majority of large defects > 30 mm cannot be meaningfully apposed by clipping. Therefore, it is unlikely that post-EMR clipping will prove to be the definitive solution to post-EMR bleeding, although in smaller lesions in high-risk patients, it appears to have a beneficial effect.

The Sydney classification for grading, the severity of deep mucosal injury (DMI) during EMR was recently published [20]. In this classification system, the severity of injury is graded from type 0 to V. Defects with the characteristic homogeneous bland blue intersecting submucosal fibers are classified as deep mucosal injury (DMI) type 0. Type III is the presence of the target sign in the resected specimen/resection bed [21] and type V representing a frank perforation with leakage of fecal matter into the peritoneal cavity. When this grading system was applied retrospectively to a cohort of 802 patients undergoing EMR of large LSL, the presence of type III, IV, or V injury was significantly associated with LSL in the transverse colon, presence of high-grade dysplasia, or submucosal invasion on histology and en bloc resection. Prophylactic clip placement in type III–V patients resulted in excellent clinical outcomes, with 85% of these patients able to be discharged home on the day of the procedure. Delayed perforation occurred in only one patient, who had type II injury. In patients

with fibrosis within the submucosal plane, evaluation for muscle injury is imperfect as the bland blue mat cannot be performed and therefore focal prophylactic clip closure to the fibrotic area is advised in this group.

Endoscopic submucosal dissection

Indications

The main advantage of ESD over EMR is the ability to perform en bloc resection of colonic lesions, largely independent of the lesion size, which is especially important for achieving R0 resection of SMIC lesions (Figs. 3 and 4). However, the main disadvantage of ESD over EMR is that it is substantially more technically challenging, requiring additional endoscopic training, increased procedure time, and multi-day hospital admission [1, 3]. The JGES recommends sufficient training in EMR, gastric/esophageal ESD, and colonoscopy techniques prior to undertaking colorectal ESD [3].

Treatment success and recurrence

In a recent systematic review of 109 studies comprising 19,484 lesions [22], the overall rate of successful en bloc resection was 91%, with successful R0 resection achieved in 82.9% of cases. Another major advantage of ESD over EMR is the lower reported rate of recurrence, with pooled recurrence rate of 2% [22]. On subgroup analysis, the pooled rates of en bloc resection and R0 resection were significantly lower and the recurrence rates were significantly higher in studies originating from Western countries, compared to those from Asia. This reflects the higher degree of ESD experience possessed by Asian endoscopists, due to gastric ESD being performed far more commonly for early gastric cancer in East Asia.

Adverse events

In a large meta-analysis, the pooled rate of bleeding was 2.7% and the rate of perforation was 5.2%, with significantly higher rates of perforation observed in studies from Western countries compared to those from Asia [22]. Overall, 1.1% of patients required surgical intervention for adverse events, with significantly higher rates of surgical intervention observed in studies from Western countries, compared to studies from Asia [22]. Nevertheless, endoscopic management of perforation using through-the-scope endoscopic clips is effective in the management of perforation during ESD. In a case-control study of 264 patients where 24 patients with perforation during ESD were matched with 240 patients without perforation, endoscopic management was successful in 95.8%, without the need for surgical intervention. On multivariate logistic regression analysis, the presence of submucosal fibrosis was the only predictor variable significantly associated with perforation during ESD, with OR 2.86 (95% CI, 1.03–7.90) [23].

Comparison of ESD with EMR

In a meta-analysis of eight studies comparing EMR with ESD for colorectal lesions, all of which originated from either Japan ($n = 6$) or South Korea ($n = 2$), the likelihood of performing en bloc resection and R0 resection was significantly higher in ESD compared to EMR, with pooled OR 6.8 (95% CI 3.3–14.2) and

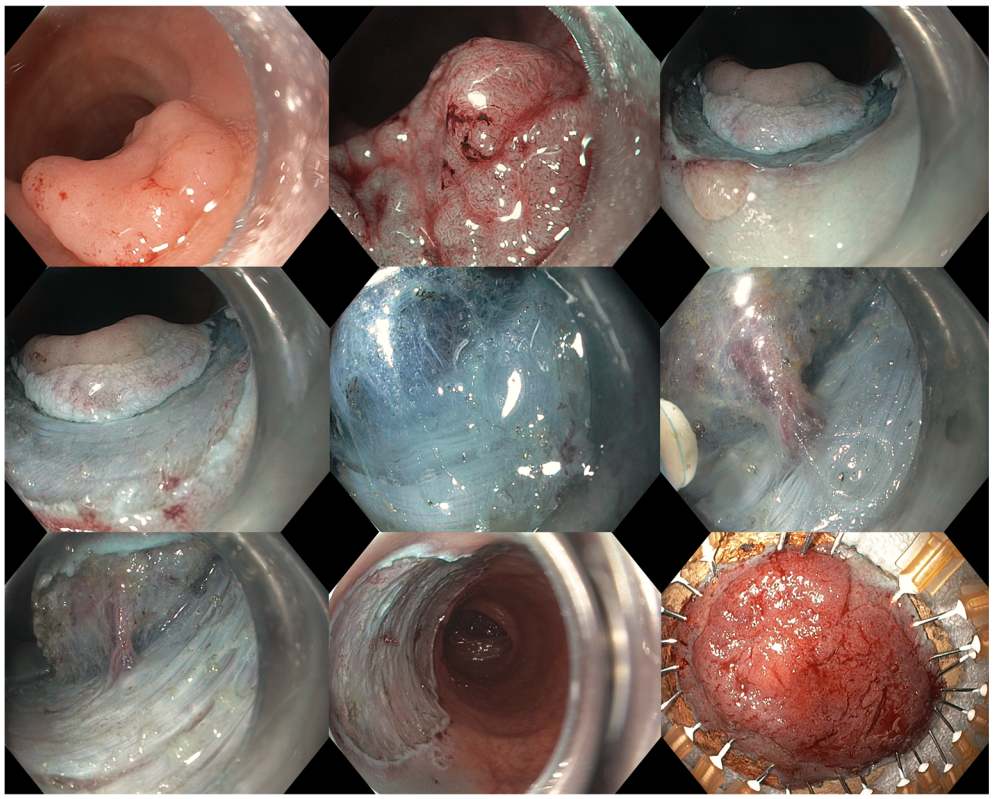

Fig. 3. ESD of a non-granular, 25 mm rectal polyp, with the Paris 0–IIa, with an area of central depression, and the Kudo IV features. The final histology showed a 1-mm adenocarcinoma arising in tubulovillous adenoma with an invasion depth of 110 μm (Sm1) and lymphovascular invasion.

4.3 (95% CI 1.7–10.7), respectively. The risk of recurrence was also significantly lower with ESD, compared to EMR (OR 0.09, 95% CI 0.04–0.21). However, ESD was more likely than EMR to take longer to complete (OR 68.1, 95% CI 36.3–79.9) and the risk of perforation was significantly higher with ESD compared to EMR (OR 4.5, 95% CI 2.5–8.1). There was however no significant difference in the risk of bleeding between the two techniques (OR 0.86, 95% CI 0.45–1.6) [24•]. Therefore ESD certainly has advantages over EMR, at the expense of longer procedure time and higher perforation risk.

In an effort to elucidate the most effective treatment modality in LSL, a cost-effective analysis was performed in over 1700 patients [25•]. In this study, the following three treatment modalities were compared: (1) EMR for all patients except for patients with suspected SMIC who were in turn referred for surgery, (2) EMR with ESD rather than surgery in patients with suspected SMIC, and (3) ESD for all patients. This study showed that the selective ESD regime was the most cost-effective treatment modality, followed by EMR for all, and lastly ESD for all patients. When compared to EMR, the selective ESD protocol resulted in avoidance of surgery in 19 patients, although only 43 ESD were performed per 1000 cases. Universal ESD was only able to reduce surgery by an additional 13 cases per 1000 and was associated with dramatic cost escalations compared to the selective ESD protocol (additional US$ 210,112 per one surgery avoided)

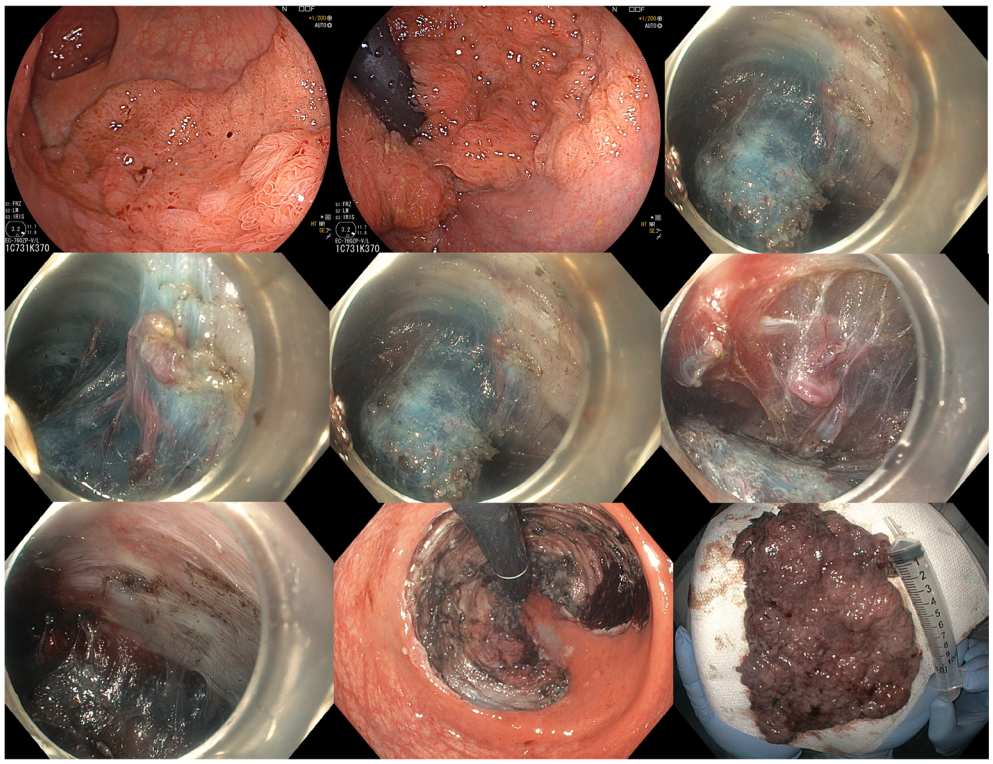

Fig. 4. ESD of a granular, 150 mm, almost circumferential rectal polyp, with the Paris 0–IIa and Kudo IV features. The final histology showed tubulovillous adenoma with low-grade dysplasia.

[25•]. Therefore, in the majority of large LSL, EMR should be the primary treatment modality and ESD should be performed in selective cases only, i.e., patients in whom SMIC is suspected.

Full-thickness resection devices

The full-thickness resection device (FTRD, Ovesco Endoscopy, Tübingen, Germany) is a novel device designed for use in patients with LSL which are difficult to remove using EMR techniques [26]. An over-the-scope-clip (OTSC) is first placed over the lesion, followed by snare resection of the lesion above the placed clip. In a prospective study from Europe comprising 181 patients with a variety of colonic lesions which included LSL that fail to lift with submucosal injection, LSL located at the appendiceal orifice/diverticulum, SMIC, and subepithelial lesions, the overall technical success was 89.5% and R0 resection rate was 76.9%, with median procedure duration of 50 min [27]. On subgroup analysis, rate of R0 resection was highest with subepithelial lesions at 87%, followed by benign LSL 77.7%; R0 resection of adenocarcinoma was however low at 44.8%. Also, R0 resection was most successful for lesions sized ≤ 9 mm at 87.5%, but low for lesions > 20 mm (58.1%). The overall adverse event rate was 9.9%, with severe adverse event rate of 4.4%, which included perforations, appendicitis and enterocolonic fistula formation. Therefore, FTRD appears to be a promising addition to the armamentarium of endoscopic treatment of LSL, especially in patients with lesions smaller than 20 mm in size.

In summary, EMR and ESD are complimentary techniques in the management of patients with precancerous lesions in the colon. EMR is safe and effective in most patients with LSL, except for SMIC lesions in whom R0 resection should be considered. Ultimately, the choice of optimal endoscopic technique for the management of LSL depends on suspicion for SMIC following lesion assessment and the availability of the requisite expertise. Selective treatment algorithms are required to optimize patient outcomes [28, 29].

Compliance with Ethical Standards

Conflict of Interest
Ji Young Bang declares that she has no conflict of interest. Michael Bourke declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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