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Clinicopathological feature and treatment outcome of patients with colorectal laterally spreading tumors treated by endoscopic submucosal dissection

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Background/Aims: Endoscopic submucosal dissection (ESD) is an advanced technique that can be used to treat precancerous and early colorectal neoplasms by facilitating *en bloc* resection regardless of tumor size. In our study, we investigated the clinicopathological feature and the treatment outcome of patients with colorectal laterally spreading tumors (LSTs) that were treated by ESD. **Methods:** The study enrolled all of 210 patients with colorectal LSTs who underwent ESD. Clinical outcomes were analyzed by retrospectively reviewing medical records. **Results:** A cancerous pit pattern (Vi/Vn) was more common in pseudo-depressed (PD) subtype than in flat elevated (FE) subtype. The incidence of adenocarcinoma in the PD subtype and nodular mixed (NM) subtypes was significantly higher than in the homogenous (HG) subtype and FE subtype. The *en bloc* and R0 resection rates were 89.0% and 85.7%, respectively. The bleeding and perforation rates were 5.2% and 1.9%, respectively. The mean procedure time was much longer in the PD subtype than in the FE subtype. The *en bloc* resection rate was significantly higher in the NM subtype than in the HG subtype. However, there were no statistically significant differences in mean procedure time, *en bloc* resection rate, R0 resection rate, bleeding rate, or perforation rate between LST-granular and LST-nongranular types. **Conclusions:** These results indicate that ESD is acceptable for treating colorectal LSTs concerning *en bloc* resection, curative resection, and risk of complications. Careful consideration is required for complete resection of the PD subtype and NM subtype because of their higher malignant potential. **(Intest Res 2019;17:127-134)**

Key Words: Colonic neoplasms; Endoscopic submucosal dissection; Outcome

INTRODUCTION

Endoscopic mucosal resection (EMR) is widely accepted and regularly used for treatment of precancerous and early colorectal neoplasms. However, this technique is not feasible and safe for *en bloc* resection if the tumor size is larger than 20 mm, as it may not facilitate accurate histologic diagnosis and reduced recurrence rates.[1-4]

Endoscopic submucosal dissection (ESD) is a recently developed therapeutic alternative to EMR. ESD has the advantages of allowing *en bloc* resection, irrespective of tumor size, location, and shape for precise histologic evaluation and reduction of local recurrence. However, ESD requires advanced technique and its procedure time is longer than EMR. Also, it has a considerable risk of complications such as bleeding and perforation, and has a long learning curve.[1-5]

Colorectal laterally spreading tumors (LSTs) are superfi-

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cial and flat neoplasm that are larger than 10 mm in diameter; LSTs have a short axis that extends laterally along the colorectal luminal wall. LSTs are divided into 2 types: the granular and the nongranular type. The granular (LST-G) type is divided into 2 subtypes: homogeneous (HG) subtype and nodular mixed (NM) subtype. The nongranular (LST-NG) type is divided into 2 types: flat elevated (FE) subtype and pseudo-depressed (PD) subtype according to their endoscopic macroscopic morphology during chromoendoscopy with indigo carmine dye spraying.[6-9]

Submucosal invasive cancer is less frequent in LSTs than in polypoid lesions of similar size.[6-9] Therefore, EMR or ESD is used to treat LSTs.[3,10-18] However, the clinicopathological characteristics of LSTs and risk of cancer are different among types and subtypes according to their endoscopic macroscopic morphology.[19-24] Submucosal invasive cancers are more frequent in the nongranular type than in the granular type. PD, NM, and larger LSTs have a higher malignant potential.[19-24] Thus, to avoid either unnecessary surgery or incomplete resection in treatment of LSTs, it is crucial to keep in mind the differences in malignant potential to select the appropriate therapeutic modality for specific LST types and subtypes.

ESD has been considered the optimal therapeutic modality for larger colorectal lesions, and the clinical outcomes of ESD in treatment of larger lesions have been reported.[1-5] However, there is lack of data about clinicopathological features of patients with LSTs treated by ESD. In this study, we investigated the clinicopathological features of patients with LSTs treated by ESD, and assessed the treatment outcomes of ESD.

METHODS

1. Patients

The study enrolled all of 210 patients with LSTs who underwent ESD at 5 university hospitals in Honam region in Republic of Korea between January 2012 and December 2013. The hospitals are affiliated with the Honam Association for the Study of Intestinal Diseases. Medical records were collected and analyzed retrospectively. Before performing ESD, we explained about the procedure and its complications such as bleeding and perforation, and obtained informed consent. The study protocol was approved by the Institutional Review Board of each participating hospitals.

2. Lesions

We defined an LST as a lesion that extends laterally along the interior luminal wall and larger than 10 mm with a low vertical axis. Morphology was categorized according to the Kudo classification using chromoendoscopy with 0.5% indigo carmine with/without magnified examination.[25] Then, we categorized the lesions into 2 types based on the endoscopic findings: LST-G and LST-NG. LST-G was further subdivided into HG subtype and NM subtype, and LST-NG was further subdivided into FE subtype and PD subtype.[9] Two endoscopists (YHJ and YEJ) blindly reviewed all cases and subdivided them into 1 of the 4 subtypes based on endoscopic images. In cases with classification discrepancies, the 2 endoscopists discussed the findings to obtain consensus and a single diagnosis. We defined transverse colon, ascending colon and cecum as proximal colon, and recto-sigmoid colon and descending colon as distal colon.

3. ESD Technique

ESD was performed using a standard single accessory-channel colonoscope (CF-H260 or PCF-Q260JI; Olympus Optical Co., Tokyo, Japan). We demarcated the lesions using chromoendoscopy with 0.4% indigo carmine dye. Then, to lift the mucosa, a mixed solution of 100 mL normal saline containing 0.4% indigo carmine and 0.0001% epinephrine was injected into the submucosal layer. A flex knife (Olympus) or flush knife (Fujinon-Toshiba ES System Co., Omiya, Japan) was used to make a circumferential mucosal incision around the lesion. The submucosal tissue under the lesion was dissected gradually with a flush knife (Fujinon), a hook knife (Olympus), an ITknife (Olympus), or a HybridKnife (ERBE Elektromedizin GmbH, Tübingen, Germany). To achieve long-lasting mucosal elevation, the normal saline–indigo carmine–epinephrine mixed solution was injected periodically during the procedure. High-frequency generators (ICC200 or VIO 300D; ERBE) were used. We performed mucosal incision about 5 mm outside the edge of the lesions in ENDO CUT mode (effect 3, output power 60–80 W for the ICC200; effect 2, duration 3, interval 3 for the VIO 300D). Mucosal incision was performed in ENDO CUT mode (effect 3, 80 W, for the ICC200), or ENDO CUT I (effect 2, duration 3, interval 3) for the VIO 300D, and submucosal dissection was performed in forced coagulation mode (effect 2, 40 W) to remove the lesion completely. We used a pair of hemostatic forceps (Coagrasper, Olympus) in soft coagulation mode (60 W) to control bleeding during the procedure or to prevent possible bleeding from visible vessels in the artificial ulcer that was made by the procedure. ESD was performed by 5 qualified endoscopists with extensive experience in performing ESD in the stomach. Ten percent buffered for-

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Table 1. Baseline Characteristics of Patients with Colorectal Laterally Spreading Tumors Undergoing Endoscopic Submucosal Dissection (n=210)

Factors	Value
Patient-related factors	
Age (yr)	65.3±10.1 (40.0–87.0)
Sex (male/female)	125 (59.5)/85 (40.5)
Smoking status (non-smoker/current or ex-smoker)	157 (74.8)/53 (25.2)
Alcohol drinking (no/yes)	148 (70.5)/62 (29.5)
BMI (kg/m^2)	24.0±2.7 (16.9–32.5)
Comorbidity (no/yes)	86 (41.0)/124 (59.0)
Hypertension (no/yes)	131 (62.4)/79 (37.6)
Diabetes mellitus (no/yes)	170 (81.0)/40 (19.0)
Aspirin or NSAIDs (no/yes)	171 (81.4)/39 (18.6)
Lesion-related factors	
Size (mm)	33.3±13.3 (10.0–130.0)
Location	
Distal colon	130 (61.9)
Recto-sigmoid colon	118 (56.2)
Descending colon	12 (5.7)
Proximal colon	80 (38.1)
Transverse colon	11 (5.2)
Ascending colon, cecum	69 (32.9)
Endoscopic morphology	
LST-G type	154 (73.3)
HG	31 (14.8)
NM	123 (58.6)
LST-NG type	56 (26.7)
FE	37 (17.6)
PD	19 (9.0)
Pit pattern (n=176)	
Non-neoplastic (type I/type II)	8 (4.5)/20 (11.4)
Adenomatous (type IIIs/type IIIL/type IV)	24 (13.6)/75 (42.6)/9 (5.1)
Cancerous (type Vi/type Vn)	25 (14.2)/15 (8.5)
Histologic grade	
Low grade dysplasia	90 (42.9)
High grade dysplasia	49 (23.3)
Adenocarcinoma	71 (33.8)
Mucosal	51 (71.8)
SM 1	15 (21.1)
SM 2	5 (7.0)
Procedure-related factors	
Procedure time (min)	60.0±55.6 (1.0–360.0)
Resection method	
En bloc resection	187 (89.0)
Piecemeal resection	23 (11.0)
Complication	
Bleeding	11 (5.2)
Perforation	4 (1.9)
Margin	
Negative	180 (85.7)
Positive	20 (9.5)
Undetermined	10 (4.8)

Values are presented as mean±SD (range) or number (%).
LST-G, laterally spreading tumor-granular; HG, homogeneous; NM, nodular mixed; LST-NG, LST-nongranular; FE, flat elevated; PD, pseudo-depressed; SM, submucosa.

malin was used to fix the resected specimen. Fixed resected specimen was then embedded in paraffin, sliced into 2-mm sections, stained with hematoxylin and eosin, and assessed microscopically. Histopathologic diagnosis was based on the World Health Organization (WHO) classification of GI epithelial neoplasia.[26] We defined a SM1 cancer as a submucosal cancer that is less than 1,000 μm below the muscularis mucosa, and a SM2 cancer as a submucosal cancer that is more than 1,000 μm below the muscularis mucosa. *En bloc* and piecemeal resections refer to resection with a single, or multiple pieces, respectively. We defined R0 resection as a specimen removed without the involvement of tumor cells in lateral and basal margins. Procedure time was counted from the beginning of local injection to the finish of lesion removal.

4. Adverse Events

Procedure-related bleeding after ESD was defined as bleeding that required transfusion or surgery, or bleeding that induced hemoglobin level to fall by 2 g/dL. Perforation was diagnosed endoscopically or by taking abdominal plain radiography or CT and see the free air.

5. Statistical Analysis

To analyze data, SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) was used; results for normally distributed continuous variables were expressed as mean±SD and categorical

variables were expressed as frequency and percentage for description. The chi-square test, Student *t*-test, or analysis of variance, as appropriate was used to analyze differences. A *P*-value of <0.05 was considered statistically significant.

RESULTS

1. Demographic and Clinical Data

We summarized the demographic and clinical data of the 210 patients in Table 1. The mean age was 65.3±10.1 years (range, 40.0–87.0 years). The study group comprised 125 males (59.5%) and 85 females (40.5%). A total of 53 patients (25.2%) had a history of smoking and 62 patients (29.5%) had a history of alcohol consumption. The mean BMI was 24.0±2.7 kg/m^2 (range, 16.9–32.5 kg/m^2). Comorbidities such as diabetes mellitus or hypertension were present in 124 patients (59.0%). Thirty-nine patients (18.6%) used medications such as aspirin and NSAIDs. The mean tumor size was 33.3±13.3 mm (range, 10.0–130.0 mm). A total 130 tumors (61.9%) were localized in the distal colon and 80 (38.1%) were in the proximal colon. LSTs were most commonly found in the recto-sigmoid colon (118, 56.2%). In order of frequency, the endoscopic macroscopic subtypes treated by ESD were as follows: NM, 123 cases (58.6%); FE, 37 cases (17.6%); HG, 31 cases (14.8%); and PD, 19 cases (9.0%). According to the Kudo pit pattern classification, 8 lesions (4.5%) were type I, 20 (11.4%) were type II, 24 (13.6%) were type IIIs, 75 (42.6%) were IIIL, 9 (5.1%) were IV, 25 (14.2%) were Vi, and 15 (8.5%) were Vn. Histologic grading revealed 90 (42.9%) low grade dysplasias, 49 (23.3%) high grade dysplasias, and 71 (33.8%) adenocarcinomas, including 51 (24.3%) mucosal and 20 (9.5%) submucosal adenocarcinomas. The mean procedure time was 60.0±55.6 minutes (range, 10.0–360.0 minutes). The *en bloc* resection rate was 89.0% (187/210). Of the 210 LSTs, 20 were diagnosed with basal or lateral margin involvement and due to difficulties in histopathological assessment, 10 could not be evaluated for completeness of resection. The R0 resection rate was 85.7% (180/210). The bleeding and perforation rates were 5.2% (11/210) and 1.9% (4/210), respectively. The complication cases including 11 bleeding and 4 perforation cases were treated by endoscopic hemoclipping, and surgery was not needed in all cases.

2. Comparison of Patient-Related Data According to Endoscopic Morphology of Colorectal LSTs

We summarized patient-related data according to endoscopic morphology of colorectal LSTs in Table 2. There were no statistically significant differences in age, sex, smoking history, alcohol use, BMI, comorbidity, or use of aspirin or NSAIDs between LST types or subtypes, but the age of patients with LST-NG were older than those with LST-G (*P*=0.034).

3. Comparison of Lesion-Related Data According to Endoscopic Morphology of Colorectal LSTs

We summarized lesion-related data according to endoscopic morphology of colorectal LSTs in Table 3. There were no statistically significant differences in tumor size or location between LST-G and LST-NG types (*P*=0.993 and *P*=0.592, respectively), but NM subtype and PD subtype tended to be larger than HG subtype and FE subtype (*P*=0.094 and

Table 2. Comparison of Patient-Related Data According to Endoscopic Appearance of Laterally Spreading Tumor Subtypes

	Granular type			Nongranular type			*P*-value
	HG (n=31)	NM (n=123)	*P*-value	FE (n=37)	PD (n=19)	*P*-value	
Age (yr)	66.5 (45–81)	63.9 (40–85)	0.208	68.0 (42–82)	67.3 (51–87)	0.815	0.034
Male sex	16 (51.6)	74 (60.2)	0.388	26 (70.3)	9 (47.4)	0.094	0.596
Smoking (yes)	8 (25.8)	32 (26.0)	0.981	11 (29.7)	2 (10.5)	0.107	0.684
Alcohol (yes)	12 (38.7)	35 (28.5)	0.268	14 (37.8)	1 (5.3)	0.009	0.600
BMI (kg/m^2)	23.5 (18.9–28.2)	23.8 (16.9–30.8)	0.594	24.9 (19.0–32.5)	23.9 (18.7–27.7)	0.247	0.055
Comorbidity	17 (54.8)	70 (56.9)	0.835	25 (67.6)	12 (63.2)	0.741	0.212
Hypertension	11 (35.5)	42 (34.1)	0.889	20 (54.1)	6 (31.6)	0.110	0.112
Diabetes mellitus	4 (12.9)	26 (21.1)	0.301	8 (21.6)	2 (10.5)	0.305	0.791
Aspirin or NSAIDs	6 (19.4)	20 (16.3)	0.681	9 (24.3)	4 (21.1)	0.784	0.297

Values are presented as mean (range) or number (%).
HG, homogeneous; NM, nodular mixed; FE, flat elevated; PD, pseudo-depressed.

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Table 3. Comparison of Lesion-Related Data According to Endoscopic Appearance of Laterally Spreading Tumor Subtypes

	Granular type			Nongranular type			*P*-value
	HG (n=31)	NM (n=123)	*P*-value	FE (n=37)	PD (n=19)	*P*-value	
Size (mm)	29.6 (15–60)	34.2 (10–130)	0.094	31.3 (11–60)	37.2 (20–70)	0.077	0.993
Location			0.021			0.029	0.592
Distal	14 (45.2)	83 (67.5)		18 (48.6)	15 (78.9)		
Proximal	17 (54.8)	40 (32.5)		19 (51.4)	4 (21.1)		
Pit pattern (n=176)			0.283			0.000	0.254
I/II	5 (20.0)	16 (15.5)		6 (20.7)	1 (5.3)		
IIIs/IIIL/IV	18 (72.0)	64 (62.1)		22 (75.9)	4 (21.1)		
Vi/Vn	2 (8.0)	23 (22.3)		1 (3.4)	14 (73.7)		
Histologic grade			0.048			0.015	0.916
Low-grade dysplasia	19 (61.3)	46 (37.4)		21 (56.8)	4 (21.1)		
High-grade dysplasia	6 (19.4)	31 (25.2)		8 (21.6)	4 (21.1)		
Adenocarcinoma	6 (19.4)	46 (37.4)		8 (21.6)	11 (57.9)		

Values are presented as mean (range) or number (%).
HG, homogeneous; NM, nodular mixed; FE, flat elevated; PD, pseudo-depressed

Table 4. Comparison of the Procedure-Related Factors According to Endoscopic Appearance of Laterally Spreading Tumor Subtypes

	Granular type			Nongranular type			*P*-value
	HG (n=31)	NM (n=123)	*P*-value	FE (n=37)	PD (n=19)	*P*-value	
Procedure time (min)	74.2 (12–330)	59.3 (3–360)	0.213	42.2 (1–185)	75.4 (20–200)	0.006	0.310
En bloc resection	24 (77.4)	113 (91.9)	0.047	32 (86.5)	18 (94.7)	0.652	0.947
Bleeding	1 (3.2)	7 (5.7)	1.000	3 (8.1)	0	0.544	1.000
Perforation	1 (3.2)	0	0.201	2 (5.4)	1 (5.3)	1.000	0.059
R0 resection	25 (80.6)	105 (85.4)	0.501	32 (86.5)	18 (94.7)	0.649	0.792

Values are presented as mean (range) or number (%).
HG, homogeneous; NM, nodular mixed; FE, flat elevated; PD, pseudo-depressed.

P=0.077, respectively). NM subtype and PD subtype were more commonly found in the distal colon, compared to HG subtype and FE subtype (*P*=0.021 and *P*=0.029, respectively). No statistically significant differences were found between LST-G and LST-NG types in frequency of a cancerous pit pattern (Vi/Vn) (*P*=0.254), but a cancerous pit pattern (Vi/Vn) was significantly more common in PD subtype than in FE subtype (*P*=0.000). There were no significant differences between LST-G and LST-NG types in the incidence of adenocarcinoma (*P*=0.916), but the incidence of adenocarcinoma in NM and PD subtypes was much higher than in HG subtype and FE subtype (*P*=0.048 and *P*=0.015, respectively).

4. Comparison of Procedure-Related Data According to Endoscopic Morphology of Colorectal LSTs

Procedure-related data according to endoscopic morphology of colorectal LSTs are summarized in Table 4. There were no statistically significant differences in mean procedure time, *en bloc* resection rate, bleeding rate, perforation rate, or R0 resection rates between LST-G and LST-NG types (*P*=0.310, 0.947, 1.000, 0.059, and 0.792, respectively), but the *en bloc* resection rate for NM subtype was significantly higher than for HG subtype (*P*=0.047). The mean procedure time was significantly longer for PD subtype than for FE subtype (*P*=0.006). In addition, the rate of perforation was higher in LST-NG type than in LST-G type (*P*=0.059).

DISCUSSION

Superficial colorectal neoplasms, including precancerous adenoma and early colorectal cancer, are now increasingly detected by screening colonoscopy and recent advances

in techniques such as chromoscopic and magnification colonoscopy.[7-9] According to recent studies, 7% to 36% of diagnosed colorectal neoplasms are flat or depressed lesions; these are usually removed by endoscopic resection, which is minimally invasive.[7-9] Colorectal LSTs are large and superficial flat neoplasms, and most are adenomatous lesions.[6-9] Therefore, colorectal LSTs are considered good candidates for endoscopic resection.[10]

EMR is useful for precancerous lesions and early superficial colorectal cancer. However, it is very hard to perform *en bloc* resection of a colorectal neoplasm that is larger than 20 mm due to snare size limitation. Large colorectal neoplasms can be removed by piecemeal EMR. However, this makes it difficult to obtain a precise histopathological diagnosis. Also incomplete resection and local recurrence rates are high in piecemeal EMR.[1-4] Therefore, EMR and piecemeal EMR are unsuitable for the treatment of colorectal neoplasms that is larger than 20 mm in diameter, including LSTs.

ESD is a practicable endoscopic procedure for large colorectal neoplasms because it provides *en bloc* specimens for accurate histopathologic diagnosis, regardless of lesion size or location, enabling precise determinations of tumor margin and invasion. However, colorectal ESD is technically difficult and has a significant risk of complications such as perforation because the colon has thin wall, sparse muscle layer, tortuous and multiple folds, and peristalsis.[1-5] Therefore, colorectal ESD is no longer widely used as a standard method for treating colorectal neoplasms, but has been applied in clinical research settings at advanced institutes. Nevertheless, previous reports showed that ESD of colorectal neoplasms was associated with a higher rate of *en bloc* resection (61.0%–98.2%) and curative resection (58.0%–95.6%), and a lower risk of recurrence (0%–11%).[5]

At first, we evaluated the efficacy and safety of ESD removal of colorectal LSTs. In our study, rate of *en bloc* resection was 89.0% and rate of R0 resection was 85.7%, with a mean size of 33.3 mm. Our results are comparable to those in previous studies,[5] and indicate that ESD provides a high rate of *en bloc* and complete resection for colorectal LSTs.

Because of recent innovations in technique and equipment, ESD has become easier and safer over time. However, compared to EMR, ESD is still associated with significant complications such as bleeding (0.5%–9.5%) and perforation (1.4%–8.2%).[5] According to our study, the bleeding rate and perforation rate after ESD were 5.2% and 1.9%, respectively, similar to those in previous reports.[5] These results suggest that ESD may be acceptable for treating large colorectal neoplasms such as LSTs because of its high rate of *en bloc* resection and curative resection, even though it is associated with significant complications such as bleeding or perforation.

Next, we compared the outcomes of ESD according to endoscopic macroscopic types and subtypes. In mean procedure time, *en bloc* resection rate, R0 resection rate, bleeding rate, or perforation rate, there were no significant differences between LST-G and LST-NG types; however, if only small perforations are considered, the frequency was higher in LST-NG than in LST-G types.

Chromo- and magnifying endoscopy with indigo carmine dye are useful for characterizing lesions based on the morphologic architecture of colonic mucosal crypt orifices (pit pattern classification).[9] Specifically, the cancerous type V pit pattern is sub-classified into type V_I and type V_N. Type V_I indicates adenoma with severe dysplasia or SM1 carcinoma and type V_N indicates invasion more than SM1. The Kudo pit pattern classification is a very precise diagnostic method that is used to predict the depth of invasion of colorectal neoplasms.[9]

Previous studies reported that the frequency of submucosal invasion by colorectal LSTs increased with size; LST-NG type had much higher rate of submucosal invasion than that of the LST-G type. Moreover, the rate of submucosal invasion by the NM subtype and PD subtype was significantly higher than that of the HG subtype and FE subtype.[19-24] In our study, no significant differences were found in frequency of cancerous pit pattern (Vi/Vn) and adenocarcinoma between LST-G and LST-NG types. However, the rate of cancerous pit pattern was significantly higher in PD subtype than in FE subtype, and tended to be higher in NM subtype than in HG subtype; moreover, the incidence of adenocarcinoma in the PD subtype and NM subtype was significantly higher than in the HG subtype and FE subtype, similar to that in previous reports.[19-24] These data suggest that different strategies may be required for treating LSTs according to their macroscopic types and subtypes. Therefore, it is critical to predict the depth of invasion by using chromo- and magnifying endoscopy, and to assess malignancy based on LST types and subtypes before selection of a therapeutic modality. If ESD is considered, these lesions must be cautiously removed *en bloc* to ensure accurate histopathological diagnosis.

A major limitation of our study is that we could not perform multivariate analyses including well-known factors related with outcomes of colorectal ESD such as fibrosis, procedure time, *en bloc* resection versus piecemeal resection, complete vs incomplete resection, and so on.

However, according to our study we can conclude that the appropriate treatment of colorectal LSTs should be deter-

mined based on their macroscopic types and subtypes, and on pit pattern findings. ESD is acceptable and promising for colorectal LSTs with regard to *en bloc* resection, curative resection, and risk of complications.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION

Conceptualization: Joo YE. Data curation: Jeong YH, Lee J, Kim SW, Seo GS, and Kim HS. Formal analysis: Jeong YH, Lee J, Kim SW, Seo GS, and Kim HS. Investigation: Jeong YH, Joo YE. Methodology and project administration: Joo YE. Resources: Jeong YH, Lee J, Kim SW, Seo GS, and Kim HS. Writing-original draft/review & editing: Joo YE.

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