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Clinical outcomes of endoscopic resection for colorectal laterally spreading tumors with advanced histology

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Abstract

Background Colorectal laterally spreading tumors (LSTs) are large, flat neoplasms that are usually treated using different endoscopic techniques based on their morphology, size, and histology. The aim of this study was to evaluate the clinical outcomes of LSTs with advanced histology treated by endoscopic resection.

Methods A total of 246 LSTs with advanced histology [i.e., high-grade dysplasia (HGD) and adenocarcinoma (AC)] treated by endoscopic resection [i.e., endoscopic mucosal resection (EMR), EMR-precutting (EMR-P), and endoscopic submucosal dissection (ESD)] were enrolled. Clinicopathological characteristics were collected by review of patient's medical records.

Results The en bloc resection and R0 resection rates were 75.6% and 85.0%, respectively. The bleeding and perforation rates were 10.2% and 2.4%, respectively. The frequency of cancerous pit pattern and bleeding was significantly higher in LSTs with AC than in LSTs with HGD. The R0 resection rate in LSTs with HGD was significantly higher than that in LSTs with AC. The frequency of cancerous pit patterns in LST cases with submucosal AC was significantly higher than those with intramucosal AC. The mean size of the LSTs was significantly larger in ESD group than in EMR or EMR-P groups. The frequencies of nodular mixed subtype, cancerous pit patterns, and en bloc resection rates were significantly higher in the ESD group than in the EMR or EMR-P groups. However, the frequency of perforation was significantly higher in EMR-P group than in EMR or ESD groups.

Conclusions These results indicate that ESD is a more acceptable treatment approach for resection of colorectal LSTs of larger size, with nodular mixed subtype, having a cancerous pit pattern or AC, using either en bloc or curative resection methods, compared to EMR or EMR-P procedures.

Keywords Laterally spreading tumor · Endoscopic resection · Advanced histology · Outcome

Endoscopic resection, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is a useful therapeutic technique for the treatment of precancerous colorectal lesions and early colorectal cancer [1–4].

Colorectal laterally spreading tumors (LSTs) are superficial large colorectal neoplasms that extend laterally with a short vertical axis along the interior luminal wall. LSTs are classified into the granular type (LST-G), including homogeneous (HG) and nodular mixed (NM) subtypes, and the non-granular type (LST-NG), including flat elevated (FE) and pseudodepressed (PD) subtypes, based on endoscopic macroscopic morphology [5, 6].

Recently, the detection of LSTs has increased due to the establishment of colonoscopy screening programs for the prevention of colorectal cancer [7–12]. These lesions are usually treated by endoscopic resection because most are

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adenomatous lesions [13–20]. However, the frequency of LSTs with advanced histology such as high-grade dysplasia (HGD) and adenocarcinoma (AC) varies according to size and the endoscopic macroscopic morphology assessment [13–20]. Previous studies have shown that larger size, the LST-NG type, and PD and NM subtypes have a higher malignant potential [13–20]. Therefore, these lesions should be removed with great caution if endoscopic resection is considered as the treatment modality for these lesions.

Because LSTs with advanced histology have a high possibility of progression by invasion and metastasis, it is clinically very important to resect LSTs with advanced histology en bloc and curatively, in order to avoid the possibility of incomplete endoscopic resections or the need for additional surgical resections. Thus, to determine the most appropriate endoscopic treatment strategy for LSTs with advanced histology, it is necessary to analyze the clinical outcomes of LSTs with advanced histology treated by endoscopic resection, for which no data are currently available.

The aim of this study was to evaluate the clinical outcomes of LSTs with advanced histology treated by endoscopic resection.

Materials and methods

Study population and lesions

Between January 2012 and December 2013, a total of 246 colorectal LSTs with advanced histology (HGD and AC) treated by different endoscopic resection procedures [i.e., EMR, EMR-precutting (EMR-P), and ESD] at five participating university hospitals in the Honam province of South Korea, affiliated with the Honam Association for Study of Intestinal Diseases (HASID), were enrolled in this study. We excluded patients with non-advanced histology [such as low-grade dysplasia (LGD), hyperplastic polyp and chronic colitis] and with lack of complete clinicopathological data. Medical records related to patients, lesions, and procedures were collected and analyzed retrospectively. According to the Kudo's classification, colorectal LSTs are classified into two types: the LST-G type, including HG and NM subtypes, and the LST-NG type, including FE and PD subtypes [12]. The cancerous pit pattern was divided into three types: non-neoplastic (type I/II), adenomatous (type IIIs/IIIL/IV), and cancerous (type Vi/Vn) [21]. Two endoscopists (J.S.J., Y.E.J.) blindly reviewed all LSTs and divided them into a single type and pit pattern based on stored endoscopic photograph images. If there was a discrepancy between two endoscopists's opinion or original endoscopy report, one type was finally selected after discussion to obtain consensus. The location of the LSTs was divided into the distal colon (rectum, sigmoid colon, and descending colon) or proximal colon (cecum, ascending colon, and transverse colon). The study protocol was approved by the Institutional Review Board of Chonnam National University Hwasun Hospital (2013-149), the Institutional Review Board of Chosun University Hospital (2014-02-005), the Institutional Review Board of Chonbuk National University Hospital (2014-01-005-002) and the Institutional Review Board of Wonkwang University Hospital (WKUH 201401-HRE-010). Prior to the endoscopic procedures, written informed consent were obtained from all patients that their clinical information could be collected for the study.

Endoscopic resection

All participating endoscopists were experts who had done more than 1000 polypectomies before. Endoscopic resection was performed using video colonoscope (Olympus CF-H260; Olympus, Tokyo, Japan) in all cases. In accordance with the patient's will and written informed consent, intravenous sedative agents (2–5 mg of midazolam and 25–50 mg of pethidine) were administered with monitoring.

EMR technique

EMR was performed using the 'lift and cut' technique. A mixture of normal saline and indigo carmine containing diluted epinephrine (1:5000–1:10,000) was injected into the submucosal layer below the lesion using a 23-gauge needle (NM-4U-1; Olympus). The lifted lesion was excised by constriction and electrical current using a snare wire (SD-12L/U-1; Olympus) and ERBE ICC 200 or VIO-300D electrocautery device (ERBE Electromedizin, Tübingen, Germany).

EMR-P technique

In EMR-P cases, a mixture of normal saline and indigo carmine with diluted epinephrine (1:5000–1:10,000) was injected into the submucosal layer below the lesion using a 23-gauge needle (NM-4U-1; Olympus), and the circumferential incision of the mucosa was performed with a flex knife (Olympus Medical Systems Co., Ltd, Tokyo, Japan). Finally, a snare (SD-9U-1 or SD-12U-1; Olympus) applied around the lesion at the mucosal circumferential incision site allowed removal of the lesion with the standard snare polypectomy technique.

ESD technique

In ESD cases, the same mixed solution described above for the EMR and EMR-P techniques was used for submucosal injections. After the submucosal injection, a circumferential mucosal incision was made around the lesion using a flex

knife (Olympus) or flush knife (Fujinon-Toshiba ES System Co., Omiya, Japan). The submucosal layer was dissected gradually with a flush knife (Fujinon), a hook knife (Olympus), or an insulated tip (IT) knife (Olympus). The resected specimen was retrieved and visible vessels in the artificial ulcer after ESD were treated with hemostatic forceps (Coagrasper, Olympus).

Histopathological assessment

The specimens resected by EMR, EMR-P, and ESD were fixed in 10% buffered formalin, paraffin-embedded, sliced into 2-mm intervals, and stained with hematoxylin and eosin, and assessed microscopically. Histopathological assessment was based on the World Health Organization classifications of gastrointestinal epithelial neoplasia [22]. HGD and AC were defined as advanced histology [22, 23]. An SM1 cancer was defined as a submucosal cancer (< 1000 μm below the muscularis mucosa), and an SM2 cancer was defined as a submucosal cancer (≥ 1000 μm below the muscularis mucosa) [22, 23].

Definition of en bloc, piecemeal, R0 resection, and procedure time

En bloc and piecemeal resections refer to a resection consisting of single and multiple pieces, respectively. Curative R0 resection was defined as a specimen removed with tumor-free lateral and basal margins. Procedure time was counted from the beginning of the local injection to the completion of removal of the lesion.

Complications

Procedure-related bleeding after EMR, EMR-P, and ESD was defined as bleeding that required transfusion or surgical intervention, or bleeding that caused hemoglobin level to fall by 2 g/dL. Perforation was diagnosed either endoscopically or by the presence of free air on abdominal plain radiograph or computed tomography.

Statistical analysis

A comparison between HGDs and ACs, intramucosal and submucosal AC, or among the treatment modalities was performed using Chi-square analysis, the Student's *t*-test, or analysis of variance, as appropriate. Descriptive analyses included proportions for categorical data as well as mean ± standard deviation (SD) for continuous data. All statistical analyses were performed with the Statistical Packages for the Social Sciences (SPSS, version 18.0; SPSS Inc., Chicago, IL, USA). A difference of $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of enrolled patients and lesions

The baseline characteristics of enrolled patients and lesions are summarized in Table 1. The mean age of the patients enrolled in the study was 66.8 ± 9.3 (range 40.0–87.0) years. This study group comprised 153 males (62.2%) and 93 females (37.8%). A total of 71 (28.9%) and 68 (27.6%) patients had a history of smoking and alcohol consumption, respectively. Medications including aspirin and NSAIDs were used in 43 patients (17.5%). The mean tumor size was 28.5 ± 11.7 mm (range 10.0–70.0) and 164 (66.7%) were localized in the distal colon and a further 82 (33.3%) were localized in the proximal colon. The most common endoscopic macroscopic subtypes were NM (130, 52.8%), followed by FE (50, 20.3%), HG (36, 14.6%), and PD (30, 12.2%). According to the Kudo's classification of cancerous pit patterns, 19 (7.7%) lesions were type I, 8 (3.3%) were type II, 16 (6.5%) were type IIIs, 64 (26.0%) were IIIL, 7 (2.8%) were IV, 37 (15.0%) were Vi, and 22 (8.9%) were Vn. Histologic grade revealed 111 (45.1%) HGDs, 103 (41.9%) intramucosal ACs, and 32 (13.0%) submucosal ACs including 23 (9.3%) SM1 and 9 (3.7%) SM2 ACs. The lesions were removed by EMR (88, 35.8%), EMR-P (39, 15.9%), and ESD (119, 48.4%). The en bloc and piecemeal resection rates were 75.6% (186/246) and 24.4% (60/246), respectively. The mean procedure time was 37.4 ± 36.8 (range 1.0–254.0) min. The R0 resection rate was 85.0% (209/246). The bleeding and perforation rates after endoscopic resection were 10.2% (25/246) and 2.4% (6/246), respectively.

Comparison of clinicopathological characteristics between LSTs with HGD and AC

The comparison of the clinicopathological characteristics of LSTs cases grouped according to HGD and AC is summarized in Table 2. With regard to patient-related variables, no statistically significant differences were found in terms of age, sex, smoking habits, alcohol consumption, or use of aspirin or NSAIDs for LSTs in the HGD or AC groups. With regard to lesion-related variables, LSTs with AC were more commonly found in the distal colon, compared to LSTs with HGD ($p = 0.001$). The frequency of a cancerous pit pattern was significantly higher in LSTs with AC than in LSTs with HGD ($p = 0.000$). No statistically significant differences were found in tumor size or endoscopic macroscopic subtypes between LSTs with

Table 1 Baseline characteristics of patients with colorectal laterally spreading tumors with advanced histology

Variable		$n=246$ (%)
Patient variables		
Age (years)	Mean ± SD (range)	66.8 ± 9.3 (40.0–87.0)
Sex	Male/female	153/93 (62.2/37.8)
Smoking status	Non-/current smoker or ex-smoker	175/71 (71.1/28.9)
Alcohol consumption	No/yes	178/68 (72.4/27.6)
Use of aspirin or NSAIDs	No/yes	203/43 (82.5/17.5)
Lesion variables		
Size (mm)	Mean ± SD (range)	28.5 ± 11.7 (10.0–70.0)
Location	Distal colon/proximal colon	164/82 (66.7/33.3)
Endoscopic type and subtype	Granular	166 (67.5)
	Homogenous	36 (14.6)
	Nodular mixed	130 (52.8)
	Non-granular	80 (32.5)
	Flat elevated	50 (20.3)
	Pseudodepressed	30 (12.2)
Pit pattern ($n=173$)	Non-neoplastic (type I/II)	19/8 (7.7/3.3)
	Adenomatous (type IIIs/IIIL/IV)	16/64/7 (6.5/26.0/2.8)
	Cancerous (type Vi/Vn)	37/22 (15.0/8.9)
Histologic grade	High-grade dysplasia	111 (45.1)
	Adenocarcinoma	135 (54.9)
	Mucosal	103 (41.9)
	Submucosa 1st layer	23 (9.3)
	Submucosa 2nd layer	9 (3.7)
Procedure variables		
Treatment modality	EMR	88 (35.8)
	EMR-P	39 (15.9)
	ESD	119 (48.4)
Resection type	En bloc resection	186 (75.6)
	Piecemeal resection	60 (24.4)
Procedure time (min)	Mean ± SD (range)	37.4 ± 36.8 (1.0–254.0)
Complete resection	Margin (−)	209 (85.0)
	Margin (+)	30 (12.2)
	Undetermined	7 (1.9)
Complications		
Bleeding	No/yes	221/25 (89.8/10.2)
Perforation	No/yes	240/6 (97.6/2.4)

SD standard deviation, *NSAIDs* non-steroidal anti-inflammatory drugs, *EMR* endoscopic mucosal resection, *EMR-P* endoscopic mucosal resection with precutting, *ESD* endoscopic submucosal dissection

HGD and AC patient groups. With regard to procedure-related variables, the R0 resection rate in LSTs with HGD was significantly higher than in LSTs with AC ($p=0.001$). The bleeding rate was significantly higher in LSTs with AC than in LSTs with HGD ($p=0.008$). No statistically significant differences were found with regard to treatment modality, en bloc resection rate, mean procedure time, or perforation rate between patient groups having LSTs with HGD or AC.

Comparison of clinicopathological characteristics between LSTs with intramucosal or submucosal AC

The comparison of the clinicopathological characteristics between LSTs with intramucosal or submucosal AC is summarized in Table 3. With regard to patient- and lesion-related variables, no statistically significant differences were found regarding age, sex, smoking habits, alcohol consumption, use of aspirin or NSAIDs, location, or endoscopic macroscopic types between LSTs

Table 2 Comparison of clinicopathological characteristics of colorectal laterally spreading tumors in high-grade dysplasia and adenocarcinoma patient groups

Variable	High-grade dysplasia $n=111$ (%)	Adenocarcinoma $n=135$ (%)	p value
Patient variables			
Age (years) (mean ± SD)	66.5 ± 9.7	67.0 ± 9.0	0.681
Male sex	67 (60.4)	86 (63.7)	0.590
Current or ex-smoker	29 (26.1)	42 (31.1)	0.391
Alcohol consumption	27 (24.3)	41 (30.4)	0.291
Use of aspirin or NSAIDs	19 (17.1)	24 (17.8)	0.892
Lesion variables			
Size (mm) (mean ± SD)	28.1 ± 11.9	28.9 ± 11.5	0.589
Location			
Distal colon	62 (55.9)	102 (75.6)	0.001
Proximal colon	49 (44.1)	33 (24.4)	
Endoscopic subtype			
Homogenous	17 (15.3)	19 (14.1)	0.086
Nodular mixed	58 (52.3)	72 (53.3)	
Flat elevated	28 (25.2)	22 (16.3)	
Pseudodepressed	8 (7.2)	22 (16.3)	
Pit pattern ($n=173$)			
Non-neoplastic (type I/II)	18 (20.2)	9 (10.7)	0.000
Adenomatous (type IIIs/IIIL/IV)	59 (66.3)	28 (33.3)	
Cancerous (type Vi/Vn)	12 (13.5)	47 (56.0)	
Procedure variables			
Treatment modality			
EMR	39 (35.1)	49 (36.3)	0.150
EMR-P	23 (20.7)	16 (11.9)	
ESD	49 (44.1)	70 (51.9)	
Resection type			
En bloc resection	86 (77.5)	100 (74.1)	0.536
Piecemeal resection	25 (22.5)	35 (25.9)	
Procedure time (min) (mean ± SD)	33.1 ± 32.1	40.9 ± 40.0	0.098
Complete resection ($n=239$)			
Margin (−)	103 (95.4)	106 (80.9)	0.001
Margin (+)	5 (4.6)	25 (19.1)	
Complications			
Bleeding (+)	5 (4.5)	20 (14.8)	0.008
Perforation (+)	3 (2.7)	3 (2.2)	1.000

SD standard deviation, *NSAIDs* non-steroidal anti-inflammatory drugs, *EMR* endoscopic mucosal resection, *EMR-P* endoscopic mucosal resection with precutting, *ESD* endoscopic submucosal dissection

with intramucosal or submucosal AC. The frequency of a cancerous pit pattern was significantly higher in LSTs with submucosal AC than in LSTs with intramucosal AC ($p=0.028$). No statistically significant differences were found in procedure-related variables including treatment modality, en bloc resection rates, mean procedure time, R0 resection rates, bleeding rates, or perforation rates between patients having LSTs with intramucosal or submucosal AC.

Comparison of clinicopathological characteristics of LSTs with advanced histology according to endoscopic treatment modality

The comparison of the clinicopathological characteristics of LSTs with advanced histology based on endoscopic treatment modality are summarized in Table 4. No statistically significant differences were found in patient-related variables including age, sex, smoking habits, alcohol

Table 3 Comparison of clinicopathological characteristics of colorectal laterally spreading tumors with high-grade dysplasia and adenocarcinoma patient groups

Variable	Intramucosal adenocarcinoma $n=103$ (%)	Submucosal adenocarcinoma $n=32$ (%)	p value
Patient variables			
Age (years) (mean ± SD)	66.5 ± 9.2	68.8 ± 8.4	0.208
Male sex	66 (64.1)	20 (62.5)	0.871
Current or ex-smoker	31 (30.1)	11 (34.4)	0.648
Alcohol consumption	31 (30.1)	10 (31.3)	0.901
Use of aspirin or NSAIDs	16 (15.5)	8 (25.0)	0.221
Lesion variables			
Size (mm) (mean ± SD)	29.54 ± 12.1	26.9 ± 9.5	0.255
Location			
Distal colon	76 (73.8)	26 (81.3)	0.391
Proximal colon	27 (26.2)	6 (18.8)	
Endoscopic subtype			
Homogenous	16 (15.5)	3. (9.4)	0.439
Nodular mixed	52 (50.5)	20 (62.5)	
Flat elevated	19 (18.4)	3 (9.4)	
Pseudodepressed	16 (15.5)	6 (18.8)	
Pit pattern ($n=84$)			
Non-neoplastic (type I/II)	6 (9.5)	3 (14.3)	0.028
Adenomatous (type IIIs/IIIL/IV)	26 (41.3)	2 (9.5)	
Cancerous (type Vi/Vn)	31 (49.2)	16 (76.2)	
Procedure variables			
Treatment modality			
EMR	41 (39.8)	8 (25.0)	0.300
EMR-P	12 (11.7)	4 (12.5)	
ESD	50 (48.5)	20 (62.5)	
Resection type			
En bloc resection	78 (75.7)	22 (68.8)	0.431
Piecemeal resection	25 (24.3)	10 (31.3)	
Procedure time (min) (mean ± SD)	38.4 ± 36.6	48.9 ± 49.3	0.197
Complete resection ($n=131$)			
Margin (−)	83 (83.0)	23 (74.2)	0.276
Margin (+)	17 (17.0)	8 (25.8)	
Complications			
Bleeding (+)	15 (14.6)	5 (15.6)	0.883
Perforation (+)	2 (1.9)	1 (3.1)	0.559

SD standard deviation, *NSAIDs* non-steroidal anti-inflammatory drugs, *EMR* endoscopic mucosal resection, *EMR-P* endoscopic mucosal resection with precutting, *ESD* endoscopic submucosal dissection

consumption, or use of aspirin or NSAIDs. With regards to lesion-related variables, the mean size of LSTs treated by ESD was significantly larger than that treated by EMR or EMR-P ($p=0.000$). The frequency of endoscopic subtypes was statistically different according to the endoscopic treatment modality used; the frequency of the NM subtype was higher with ESD (63.9%) than with EMR (43.2%) or EMR-P (41.0%) ($p=0.001$) treatment modalities. The frequency of the cancerous pit pattern was significantly higher with ESD or EMR-P than with EMR ($p=0.000$). The frequency of location and histologic grade was not statistically different with regard to the endoscopic treatment modality. In terms of procedure-related variables, the en bloc resection rate was significantly higher for ESD than for EMR or EMR-P ($p=0.000$). The mean procedure time was significantly longer for ESD than for EMR or EMR-P ($p=0.000$). The frequency of perforation was significantly higher with EMR-P than with EMR- or ESD-treated cases ($p=0.032$). The R0 resection and bleeding rates did not differ statistically according to the endoscopic treatment modality.

Table 4 Comparison of clinicopathological characteristics of colorectal laterally spreading tumors according to treatment modality

Variable	EMR $n=88$ (%)	EMR-P $n=39$ (%)	ESD $n=119$ (%)	p value
Patient variables				
Age (years) (mean ± SD)	68.3 ± 8.8	66.9 ± 8.4	65.7 ± 9.9	0.135
Male sex	57 (64.8)	28 (71.8)	68 (57.1)	0.215
Current or ex-smoker	33 (37.5)	9 (23.1)	29 (24.4)	0.080
Alcohol consumption	27 (30.7)	9 (23.1)	32 (26.9)	0.654
Use of aspirin or NSAIDs	15 (17.0)	8 (20.5)	20 (16.8)	0.875
Lesion variables				
Size (mm) (mean ± SD)	22.3 ± 9.0	25.0 ± 8.3	34.3 ± 11.6	0.000
Location				
Distal colon	55 (62.5)	22 (56.4)	87 (73.1)	0.097
Proximal colon	33 (37.5)	17 (43.6)	32 (26.9)	
Endoscopic subtype				
Homogenous	21 (23.9)	3 (7.7)	12 (10.1)	0.001
Nodular mixed	38 (43.2)	16 (41.0)	76 (63.9)	
Flat elevated	20 (22.7)	14 (35.9)	16 (13.4)	
Pseudodepressed	9 (10.2)	6 (15.4)	15 (12.6)	
Pit pattern ($n=173$)				
Non-neoplastic (type I/II)	13 (31.7)	0 (0.0)	14 (14.9)	0.000
Adenomatous (type IIIs/IIIL/IV)	22 (53.7)	23 (60.5)	42 (44.7)	
Cancerous (type Vi/Vn)	6 (14.6)	15 (39.5)	38 (40.4)	
Histologic grade				
High-grade dysplasia	39 (44.3)	23 (59.0)	49 (41.2)	0.155
Adenocarcinoma	49 (55.7)	16 (41.0)	70 (58.8)	
Depth of invasion in adenocarcinoma ($n=135$)				
Mucosal	41 (83.7)	12 (75.0)	50 (71.4)	0.300
Submucosal	8 (16.3)	4 (25.0)	20 (28.6)	
Procedure variables				
Resection type				
En bloc resection	62 (70.5)	20 (51.3)	104 (87.4)	0.000
Piecemeal resection	26 (29.5)	19 (48.7)	15 (12.6)	
Procedure time (min) (mean ± SD)	17.5 ± 21.5	26.8 ± 19.0	55.5 ± 41.1	0.000
Complete resection ($n=239$)				
Margin (−)	71 (81.6)	36 (92.3)	102 (90.3)	0.112
Margin (+)	16 (18.4)	3 (7.7)	11 (9.7)	
Complications				
Bleeding (+)	14 (15.9)	2 (5.1)	9 (7.6)	0.082
Perforation (+)	0 (0.0)	3 (7.7)	3 (2.5)	0.032

SD standard deviation, *NSAIDs* non-steroidal anti-inflammatory drugs, *EMR* endoscopic mucosal resection, *EMR-P* endoscopic mucosal resection with precutting, *ESD* endoscopic submucosal dissection

Discussion

Most colorectal cancers commonly develop from precursor lesions defined as adenomatous polyps. Currently, screening programs for colorectal cancer have been carried out using either fecal occult blood tests, flexible sigmoidoscopy or colonoscopy, and colonoscopic polypectomy for precancerous lesions. The detection of early colorectal cancers detected in these screening programs has reduced the incidence of colorectal cancer and mortality [24–26].

Recently, the diagnoses of colorectal LSTs have gradually increased due to a wider implementation of screening colonoscopy programs, and the recent advances in endoscopic techniques and devices [11, 12]. Most LSTs are precancerous adenomatous lesions and are usually resected endoscopically to prevent progression towards colorectal cancer [13–20]. In particular, colorectal LSTs with advanced histology should be resected completely and curatively because of the high possibility of cancer progression. Thus, it is important to evaluate the clinical

outcomes of LSTs with HGD or AC treated by endoscopic resection.

In our study, 66.7% of LSTs with advanced histology were localized in the distal colon. Also, LSTs with AC were more commonly found in the distal colon, as compared to LSTs with HGD. The most common location of sporadic colorectal cancers has been reported to be the rectosigmoid colon and about half of sporadic colorectal cancers are within reach of a flexible sigmoidoscope [24–26].

In our study, the en bloc resection rate for LSTs with advanced histology was 75.6%. The R0 resection rate was 85.0%. As shown by many previous reports, endoscopic resection of LSTs is successful in 70–100% of cases [13–20]. Our en bloc resection and R0 resection rates were similar to those of previous reports [13–20]. The R0 resection rate in LSTs with HGD was significantly higher than that in LSTs with AC. This result indicates that endoscopic resection of precancerous lesions is more effective as a curative resection modality than endoscopic resection of cancerous lesions.

In the cancerous pit pattern analysis, the frequency of pit patterns was significantly higher in LSTs with AC than in those with HGD. Also, the frequency of cancerous pit patterns in LSTs with submucosal AC was significantly higher than in those with intramucosal AC. In previous studies, the Kudo's pit pattern classification has been used as a reliable and accurate method for the differentiation of neoplastic and non-neoplastic colorectal lesions and has been shown to be useful for distinguishing between intramucosal and submucosal cancers [27–29]. Furthermore, the cancerous pit pattern is a risk factor for predicting deep submucosal invasion (i.e., $\geq$ 1000 μm below the muscularis mucosa) in colorectal LSTs [30].

The frequency of bleeding was also significantly higher in LSTs with AC than in LSTs with HGD. A possible explanation might be that AC represents rapid tumor cell growth and is supported by neoangiogenesis.

In the comparison analysis of treatment modalities, the mean size of LSTs was significantly larger in cases treated with ESD than in cases treated with EMR or EMR-P, and the en bloc resection rate was significantly higher in those treated with ESD than in those treated with EMR or EMR-P. It has been shown previously that colorectal neoplasms up to 20 mm in size can be removed en bloc by EMR. However, if the tumor size is larger than 20 mm, this technique is not feasible and safe due to the size limitation of the snare [1–4]. ESD is an advanced technique for the treatment of large colorectal neoplasms providing en bloc resection suitable for accurate histopathological evaluation, regardless of tumor size [1–4].

In our study, the most common endoscopic macroscopic morphology of LSTs with advanced histology was the NM subtype. The frequency of the NM subtype and cancerous pit pattern was significantly higher in cases treated with ESD than in those treated with EMR-P or EMR. Previous studies have shown that LSTs with larger size, cancerous pit pattern, NG type, PD, and NM subtypes had a higher malignant potential [5–12]. Therefore, for these lesions, it is necessary to choose the most suitable endoscopic treatment modality, which allows an accurate pathologic assessment and reduced incidence of local recurrence. Most endoscopists tend to select ESD in the therapeutic management of large colorectal neoplasms with a high malignant potential for en bloc and curative resection [31–33].

Bleeding and perforation are the most common complications occurring after endoscopic resection [1–4]. In our study, overall bleeding and perforation rates were 10.2% and 2.4%, respectively, which was similar to those of previous reports [1–4]. The frequency of bleeding did not differ statistically according to the endoscopic treatment modality. The frequency of perforation was significantly higher in patients treated with EMR-P than in those who underwent EMR or ESD. EMR-P is a modified EMR technique, in which snaring and resection are performed around the lesion at the mucosal incision site without dissecting the submucosal layer after the circumferential incision of the lesion mucosa using an ESD knife. However, it was interpreted within the limitation of small perforation cases. Further larger studies are needed to confirm this finding.

Our study has a limitation. We have not reported long-term follow-up data including recurrence after endoscopic resection. It is important to evaluate the efficacy and prognosis of endoscopic resection for LSTs with advanced histology. A previous report has shown that intramucosal and submucosal colorectal cancer with depth of invasion in the submucosa < 1000 μm have a good prognosis and curative resection could be expected after endoscopic resection. However, recurrence can occur in deep submucosal cancers [34–36]. In our study, there were 32 cases of LSTs with submucosal AC including 23 SM1 and 9 SM2 ACs, and all of the latter cases underwent subsequent surgical resection.

In conclusion, our study shows that we may consider ESD as a more acceptable treatment approach for the resection of colorectal LSTs of larger size, with the nodular mixed subtype, having a cancerous pit pattern or AC, using either en bloc or curative resection, when compared to EMR or EMR-P procedures.

Compliance with ethical standards

Disclosures Jin-Sung Jung, Ji-Yun Hong, Hyung-Hoon Oh, Sun-Seog Kweon, Jun Lee, Sang-Wook Kim, Geom-Seog Seo, Hyun-Soo Kim, and Young-Eun Joo have no conflicts of interest or financial ties to disclose.

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