

# Usefulness and feasibility of endoscopic submucosal dissection for colorectal tumor: a nationwide multicenter retrospective study in Korea

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**Background:** Detection rate of precursor lesion of colorectal cancer and early colon cancer have recently been rising because of increased screening endoscopy and increased incidence of colorectal cancer. Endoscopic submucosal dissection (ESD) technique has been reported to be useful in the treatment of such superficial lesions in colon. However, nationwide multicenter study for usefulness and feasibility of colorectal ESD is still limited.

**Methods:** From January 2009 to February 2014, colorectal ESD data performed at nationwide university hospitals were enrolled in retrospective design. Demographic, clinical, technical data, and data of complications were reviewed.

**Results:** A total of 189 patients were included with 191 lesions resected by colorectal ESD. The indications were epithelial lesions (n=120), neuroendocrine tumor (n=25), cancer (n=46). The lesion locations were right colon (n=45), transverse colon (n=17), descending colon (n=8), sigmoid colon (n=33), rectum (n=88). The median size of the lesions was 21.1 mm. En bloc resection rate of the lesion was 83.3%, with complete R0 resection in 73.3%. The median duration of ESD was 53.7 minutes. Factor related to En bloc resection was tumor location (right colon/transverse colon 72.6% vs. other location 89.2%, P=0.004). Factors related complication were tumor location (right colon/transverse colon 12.9% vs. Other location 10.13%, P=0.044) and tumor size (without complication 20.5±10.2 mm vs. with complication 25.9±11.7 mm, P=0.027). The short term morbidity rate was 11.0% including 5 hemorrhages (2.6%) and 16 perforations (8.4%).

**Conclusions:** In this study, ESD shows promise as a useful, potentially feasible procedure in colorectal superficial tumor because of high en bloc resection rate and low morbidity rate, especially in small lesions located from descending colon to rectum.

**Keywords:** Endoscopic submucosal dissection (ESD); colorectal superficial tumor; distal colon

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## Introduction

Early superficial gastrointestinal cancer is defined as cancer invasion limited to mucosal or submucosal layers. Until recently surgery was the cornerstone treatment for superficial/early gastrointestinal tumors. Diagnosis rate of precursor lesion of colorectal cancer and early stage colorectal cancer have been increasing rapidly because of increased screening gastrointestinal endoscopies in Korea (1). This trend has also resulted in advances in the therapeutic endoscopy, that is less invasive than surgery. More recently, endoscopic submucosal dissection (ESD) is feasible method in treating early gastric cancer (2). This technique enables en bloc resection of larger than 20mm, leading to exact histologic evaluation of the specimen and low recurrence rate (3-5). However, this technique in colorectal area is not widely used because of technical difficulty, a protracted procedure time, and the risk of complications accompanying the procedure such as perforation, bleeding (4). In Korea, colorectal ESD is performed as actively as in Japan. Although there are some single-center studies about feasibility of colorectal ESD came from Japanese experts (4,6-9), nationwide multicenter study for effectiveness and feasibility of colorectal ESD is still limited. The aim of this study is to investigate the usefulness and feasibility of ESD in colorectum performed by various experienced endoscopists from multiple university hospitals in Korea.

## Methods

ESD database performed for colorectal neoplasia from January 2009 to October 2015 at six university hospitals in Korea were investigated retrospectively under IRB approval.

All the lesions that were node-negative cancer or premalignant neoplasia and were technically unsuitable for en bloc resection by conventional endoscopic mucosal resection (EMR) were considered suitable for ESD. We investigated medical records, including demographic, clinical, technical data, and data of immediate complications. The rates of en bloc resection, the incidence of complications, and procedure times were analyzed. The factors analyzed in relation to procedure complications were the tumor location and size, and the final histological data (tumor type and stage).

Endoscopic ultrasound and/or computed tomography (CT) scan examinations were carried out before treatment whenever they were considered to be useful, particularly in

cases of cancer. CT scans were carried out in cancer patients (n=47) and carcinoid patients (n=25). EUS were carried out in only over 1cm sized carcinoid tumor (n=8). All patients gave informed consent before undergoing ESD.

## ESD

A single-channel video colonoscope (CF type Q260AI with variable hardness; Olympus Optical Co, Ltd, Tokyo, Japan) usually with air rather than CO<sub>2</sub> insufflation was used in this study. Transparent hood was attached to the tip of endoscopy to apply tension to the submucosal layer to enable easy entry of the endoscope into the submucosal layer and to stabilize knife handling during dissection. Peripheral marking using argon plasma coagulation was done after identification of the lesion with chromoendoscopy with indigo carmine.

Glycerol mixture solution (10% glycerol 15 mL + 1% hyaluronic acid 5 mL + 1% epinephrine 0.2 mL + 0.4% indigo carmine 0.2 mL) injected to submucosal layer to elevate the lesion from muscle layer. Flex-knife or Dual-knife was used for circumferential incision, and then submucosal dissection was performed with a variety of knives, including: Flex-knife, IT-knife, Dual-knife, Hook-knife (all Olympus Corp., Tokyo, Japan). Mucosal incision was done with the endocut mode (e.g., endocut I, effect 2, duration 3, interval 2 in VIO300D), and then submucosal dissection was done with coagulation mode (e.g., Forced coagulation, Output 40W, effect 2 in VIO300D). During ESD, either various knives used for dissection or hemostatic instrument such as Coagrasper (Olympus Corp., Tokyo, Japan) was used for hemostasis. If perforation was developed during procedure, hemoclip was applied. After the ESD, preventive endoscopic hemostasis was undertaken when deemed useful for any oozing or exposed vessel by using the same instruments as used during intra-operative hemostasis. If there was lateral resection involvement or deep resection margin involvement, the additional resection were made in later sitting.

## Statistical analysis

Differences in categorical variables were evaluated by Fisher's exact test or chi-square test. For comparison of continuous variables, Mann-Whitney U test were used. Univariate analysis was performed to analyze factors (location, tumor size) related short term clinical outcomes (En bloc resection, complication, procedure

**Table 1** Clinicopathological characteristics of colorectal endoscopic submucosal dissection

Characteristics	n=191
Age (mean ± SD), years	61.1±11.8
Sex, n (%)	
Male	118 (61.8)
Female	73 (38.2)
Co-morbidities, n (%)	89 (46.6)
Recent antiplatelet agent use, n (%)	25 (13.1)
Tumor size (mean ± SD), mm	21.1±10.4
Location of tumors, n (%)	
Rectum	88 (46.1)
Sigmoid colon	33 (17.3)
Descending colon	8 (4.2)
Transverse colon	17 (8.9)
Ascending colon	45 (23.6)
Macroscopic tumor type, n (%)	
LST	140 (73.3)
Protruding	51 (26.7)
Histologic finding, n (%)	
Adenoma	
Low grade dysplasia	62 (32.5)
High grade dysplasia	51 (26.7)
Adenocarcinoma	
T1m cancer	34 (17.8)
T1sm cancer	12 (6.3)
Neuroendocrine tumor (Carcinoid)	25 (13.1)
Hyperplastic polyp	7 (3.7)
Resection method, n (%)	
ESD only	125 (65.4)
ESD with snaring	66 (34.6)
En bloc resection, n (%)	160 (83.8)
Complete resection, n (%)	140 (73.3)
Procedure time (mean ± SD), min	53.7±46.0
Complication, n (%)	
Perforation	16 (8.4)
Bleeding	5 (2.6)

LST, lateral spreading tumor; ESD, endoscopic submucosal dissection.

time). Multivariate analysis was performed using a logistic regression model [En bloc resection, location of tumor (Other colon), Macroscopic type (protruding), ESD only]. Odds ratios and 95% confidence intervals were calculated to evaluate predictors of perforation. P value of <0.05 were considered statistically significant.

## Results

### *Clinicopathological features*

During the study period, a total of 189 patients were included with 191 lesions resected by ESD. The mean age of the patients was 61.1±11.8 years, and the male/female ratio was 1.62 (118/73). The mean size of the tumors was 21.1±10.4 mm. The majority of the lesions were located in rectum (n=88, 46.1%). The others were located in right colon (n=45, 23.6%), sigmoid colon (n=33, 17.3%), transverse colon (n=17, 8.9%), and descending colon (n=8, 4.2%). In 46 patients (24.1%) the indication for ESD was adenocarcinoma. Data on tumor location and size, indication for ESD, histological type, and tumor infiltration are presented in *Table 1*.

### *Curability*

En bloc resection was achieved for 160 of the 191 lesions (83.8%). The lesions for which en bloc resection could not be achieved located in right colon/transverse colon 17/62 (27.4%) *vs.* other location 14/129 (10.9%) (*Tables 2,3*). The final pathology results showed low grade dysplasia in 32.5% (62/191), followed by high grade dysplasia in 26.7% (51/191), adenocarcinoma in 24.1% (46/191), neuroendocrine tumor in 13.1% (25/191). The overall complete resection rate was 73.3% (140/191) (*Table 4*). Lateral resection involvement was 22.0% (42/191), managed by additional resection or ablation with argon plasma coagulation. Deep resection margin involvement was 4.2% (8/191), two are cancers, others are carcinoids.

### *Procedure time*

The median procedure time was 53 minutes, with a mean of 53.7±46.0 minutes. Small lesions (<20 mm) required less time for resection compared with larger ones (>20 mm) (mean 35.7±22.6 *vs.* 94.8±66.2 minutes; P<0.0001). Also, complicated ESDs had a significantly longer procedure time than uncomplicated ESDs (mean 96.8±57.6 *vs.*

**Table 2** Factors related to en bloc resection

Factors	En bloc resection		P value
	Yes (n=160)	No (n=31)	
Age (mean ± SD), years	61.1±11.9	61.1±11.3	0.997
Sex (men), n (%)	99 (61.9)	19 (61.3)	0.951
Co-morbidities, n (%)	73 (45.6)	16 (51.6)	0.541
Recent Antiplatelet agent use, n (%)	21 (13.1)	4 (12.9)	0.973
Tumor size, mm, mean ± SD	20.7±10.9	23.4±7.4	0.091
Location of tumors, n (%)			0.004
Right side colon and transverse colon	45 (28.1)	17 (54.8)	
Other colon	115 (71.9)	14 (45.2)	
Macroscopic type, n (%)			0.025
LST	112 (70.0)	28 (90.3)	
Protruding	48 (30.0)	3 (9.7)	
Histologic finding, n (%)			0.041
Adenoma	88 (55.0)	25 (80.6)	
Cancer	41 (25.6)	5 (16.1)	
Carcinoid	24 (15.0)	1 (3.2)	
Hyperplastic polyp	7 (4.4)	0 (0.0)	
Resection method, n (%)			0.003
ESD only	112 (70.0)	13 (41.9)	
ESD with snaring	48 (30.0)	18 (58.1)	
Procedure time, min, mean ± SD	51.9±45.8	62.90±46.4	0.225

LST, lateral spreading tumor; ESD, endoscopic submucosal dissection.

**Table 3** Predictive factors related en bloc resection (multivariate analysis)

Predictive factors	Adjusted OR	95% CI for adjusted OR	P value
Location of tumors (other colon)	2.238	0.981–5.109	0.056
Macroscopic type (protruding)	3.215	0.892–11.590	0.074
ESD only	2.955	1.308–6.676	0.009

ESD, endoscopic submucosal dissection.

**Table 4** Factors related to complete resection

Factors	Complete resection		P value
	Yes (n=140)	No (n=50)	
Age (mean ± SD), years	60.9±12.0	62.0±11.3	0.585
Sex (men), n (%)	88 (62.9)	29 (58.0)	0.544
Co-morbidities, n (%)	66 (47.1)	22 (44.0)	0.702
Recent antiplatelet agent use, n (%)	20 (14.3)	5 (10.0)	0.442
Tumor size, mm, mean ± SD	20.5±10.2	22.6±11.2	0.227
Location of tumors, n (%)			0.554
Right side colon and transverse colon	44 (31.4)	18 (36.0)	
Other colon	96 (68.6)	32 (64.0)	
Macroscopic type, n (%)			0.017
LST	96 (68.6)	43 (86.0)	
Protruding	44 (31.4)	7 (14.0)	
Histologic finding, n (%)			0.005
Adenoma	74 (52.9)	39 (78.0)	
Cancer	41 (29.3)	4 (8.0)	
Carcinoid	18 (12.9)	7 (14.0)	
Hyperplastic polyp	7 (5.0)	0 (0.0)	
Resection method, n (%)			0.076
ESD only	87 (62.1)	38 (76.0)	
ESD with snaring	53 (37.9)	12 (24.0)	
Procedure time, min, mean ± SD	49.0±41.0	66.9±56.4	0.044

LST, lateral spreading tumor; ESD, endoscopic submucosal dissection.

48.7±41.8 minutes; P=0.002).

### Complication

There were no deaths in patients who were enrolled this study. We assessed predictive factor of perforation using variables as tumor location, tumor size, procedure time. Perforation were observed in 16 of 191 cases (8.4%). All perforations were treated by endoscopic hemoclipping during initial ESD procedures. Eleven out of 16 cases of perforation needed surgical intervention due to ineffective

**Table 5** Factors related to complication

Factors	Complication		P value
	Yes (n=21)	No (n=170)	
Age (mean ± SD), years	62.4±10.7	61.0±11.93	0.609
Sex (men), n (%)	12 (57.1)	106 (62.4)	0.643
Co-morbidities, n (%)	9 (42.9)	80 (47.1)	0.716
Recent antiplatelet agent use, n (%)	2 (9.5)	23 (13.5)	1.000
Tumor size, mm, mean ± SD	25.9±11.7	20.5±10.2	0.027
Location of tumors, n (%)			0.559
Right side colon and transverse colon	8 (38.1)	54 (31.8)	
Other colon	13 (61.9)	116 (68.2)	
Macroscopic type, n (%)			0.069
LST	19 (90.5)	121 (71.2)	
Protruding	2 (9.5)	49 (28.8)	
Histologic finding, n (%)			0.591
Adenoma	15 (71.4)	98 (57.6)	
Cancer	4 (19.0)	42 (24.7)	
Carcinoid	1 (4.8)	24 (14.1)	
Hyperplastic polyp	1 (4.8)	6 (3.5)	
Resection method, n (%)			0.272
ESD only	16 (64.1)	109 (76.2)	
ESD with snaring	5 (35.9)	61 (23.8)	
Procedure time, min, mean ± SD	96.8±57.6	48.7±41.8	0.002

LST, lateral spreading tumor; ESD, endoscopic submucosal dissection.

clipping. Two cancer cases were underwent segment. 9 high grade dysplasia or low grade dysplasia cases underwent primary suture. The other 5 perforations (31.3%) were treated supportively, without surgical treatment, by NPO and giving antibiotics intravenously, with favorable outcomes (Table 5).

Significant ESD-related bleeding needed follow up endoscopy and endoscopic hemostasis involving endoclipping and electrocautery occurred in 5 cases (2.6%). No case required surgical intervention for post-ESD bleeding.

### Factors related to short term clinical outcomes

The relationship among tumor location, tumor size, en bloc resection rate, complication rate, and procedure time was investigated. Multivariate logistic regression analysis was performed to evaluate predictive factor in en bloc resection. The analysis showed that proximal location was possible predictive factor (OR: 2.238, 95% CI: 0.981–5.109, P=0.056).

### Discussion

Development of endoscopic technology and skill enables minimally invasive strategy in managing a superficial large gastrointestinal tumor. ESD is the one of the minimally invasive treatment for gastrointestinal tumor. ESD technique has higher en bloc resection rate than conventional EMR methods, facilitates accurate histopathological evaluation and reduces tumor recurrences (10,11). ESD has recently been reported to be useful and safe in the treatment of large superficial gastrointestinal tumor in Japan, because it provides a higher en bloc resection rate and is less invasive than surgical resection (7,11-13). However, ESD in colorectal tumor has not been widely performed because technical difficulty of colon ESD is very high because of characteristic of the colon (thin wall and existence of peristalsis, fold, flexion, fecal fluid) and the risk of complication such as perforation is higher than stomach. Although there were several single center studies about ESDs for colorectal neoplasm in Korea, this is the first nationwide Korean multicenter study for colon ESD.

En bloc resection rate in colon ESD has been reported about above 90% in Japan (14-16), 70% in Europe (17). In our multicenter study, the en bloc resection rate was 83.8%, similar to Japanese study. En bloc resection rate was lower in right colon and transverse colon than other colon location. It may result from operational difficulty in proximal colon. However, perforation rate is slightly higher than previous study in Japan.

The bleeding rate of 2.6%, was similar to most published series (3,7). We performed hemostasis on all vessels likely to bleed or actively bleeding, regardless of the location, if we could possibly do so, as it has already been shown that preventive coagulation of visible vessels in the resection area after ESD might decrease bleeding (18). All cases were successfully managed by conservative medical treatment with no need for surgery, and it can be considered a minor matter of concern that is likely to improve with experience.

The perforation is a trappy complication, especially in colon ESD, even in the hands of an expert endoscopist. Our study showed that perforation rate was 8.4%, slightly higher than previous study (3,7). Reluctance to perform colon ESD results from mostly perforation which may need emergent surgery. However, iatrogenic perforation during ESD procedure can be managed by endoscopic intervention and conservative management including fasting and antibiotics. Fujimoto reported that nonsurgical method including immediate endoclip closure and conservative strategy during ESD is feasible option treating iatrogenic perforation. In our study, 16 iatrogenic perforation was developed during ESD and 5 perforations were managed successfully by endoscopic intervention and conservative management while 11 case needed emergent surgery. Tumor location was an important factor predicting perforation during ESD in our study. In ESD at proximal colon, we should perform ESD carefully paying attention to perforation.

ESD procedure time is one important drawback of ESD. The procedure time in ESD is usually longer than conventional EMR, especially in colon. In our study, median procedure time was 53 minutes, shorter than European group, 105 minutes (17). We found that patient that take longer procedure time in ESD had more complication and large lesion tended to take longer time.

In summary, ESD as a new method shows promise or potential as a useful, potentially feasible procedure in colorectal superficial tumor because of high en bloc resection rate and low short term morbidity rate, especially in small lesions located from descending colon to rectum. However, as the study by Fujiya *et al.*, in large lesion of proximal colon, the ESD procedure was longer, and the rate of additional surgery and perforation was higher, suggesting that indications for ESD should be rigorously determined in order to avoid such problems (19). In case of early colorectal cancer, it would be better to consider ESD prior to operation since ESD is less invasive than operation. Long-term outcome remains to be elucidated by a large-scale, prospective study.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* ESD database performed for colorectal neoplasia from January 2009 to October 2015 at six university hospitals in Korea were investigated retrospectively under IRB approval and written informed consent was obtained from all patients.

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